

EXHIBIT A

free merchandise from other merchandise in the sales or crib area.

(3) *Exception to marking requirement.* If the proprietor has an electronic inventory system capable of immediately identifying other merchandise from conditionally duty-free merchandise, the proprietor need not separate domestic merchandise and merchandise which was previously entered or withdrawn for consumption from conditionally duty-free merchandise or mark the merchandise.

PART 144—WAREHOUSE AND REWAREHOUSE ENTRIES AND WITHDRAWALS

5. The general authority citation and specific authority citation for part 144 continue to read as follows:

Authority: 19 U.S.C. 66, 1484, 1557, 1559, 1624.

* * * * *
Section 144.37 also issued under 19 U.S.C. 1555, 1562.

6. In § 144.37:

a. Paragraph (a) is amended by removing the word "shall" each place it appears and, in its place, adding the word "must"; and by removing the word "Customs" each place it appears and, in its place, adding the term "CBP".

b. Paragraphs (b)(1), (f), and (h)(3) are amended by removing the word "shall" each place it appears and, in its place, adding the word "must".

c. In paragraph (b)(2), the first sentence is amended by removing the word "shall" and, in its place, adding the word "must" and by removing the reference to "Customs" and, in its place, adding the term "CBP"; the second and third sentences are amended by removing the word "shall" each place it appears and, in its place, adding the word "will"; and the last sentence is amended by removing the word "shall" and, in its place, adding the word "must".

d. Paragraph (d) is amended by removing the word "Customs" each place it appears and, in its place, adding the term "CBP"; and by removing the word "shall" each place it appears and, in its place, adding the word "must".

e. Paragraphs (h)(2) introductory text and (h)(2)(vi) are revised to read as follows:

§ 144.37 Withdrawal for exportation.

* * * * *

(h) * * *
(2) *Sales ticket content and handling.* Sales ticket withdrawals must be made only under a blanket permit to withdrawal [see § 19.6(d) of this

chapter] and the sales ticket will serve as the equivalent of the supplementary withdrawal. A sales ticket is an invoice of the proprietor's design which will include:

* * * * *
(vi) A statement on the original copy (purchaser's copy) to the effect that goods purchased in a duty-free store will be subject to duty and/or tax with personal exemption if returned to the United States. At the time of purchase, the original sales ticket must be made out in the name of the purchaser and given to the purchaser. One copy of the sales ticket must be retained by the proprietor. This copy may be maintained electronically provided the port director is satisfied that the proprietor has the ability to print the sales ticket upon the request of a CBP officer. A permit file copy will be attached to the parcel containing the purchased articles unless the proprietor has established and maintained an effective method to match the parcel containing the purchased articles with the purchaser. Additional copies may be retained by the proprietor.

* * * * *

W. Ralph Basham,
Commissioner, U.S. Customs and Border Protection.

Approved: January 10, 2008.

Timothy E. Skud,
Deputy Assistant Secretary of the Treasury.
[FR Doc. E8-522 Filed 1-15-08; 8:45 am]
AILING CODE 9111-14-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314, 601, and 814

[Docket No. 2008N-0021]

Supplemental Applications Proposing Labelling Changes for Approved Drugs, Biologics, and Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations regarding changes to an approved new drug application (NDA), biologics license application (BLA), or medical device premarket approval application (PMA) to codify the agency's longstanding view on when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review

of such change. FDA is proposing to reaffirm its longstanding position that a supplemental application submitted under those provisions is appropriate to amend the labeling for an approved product only to reflect newly acquired information, as well as to clarify that such a supplemental application may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or device. The amendments proposed by this document are intended to reflect the agency's existing practices with respect to supplemental applications submitted to FDA.

DATES: Submit written or electronic comments on the amendments proposed by this document by March 17, 2008. See section VIII of this document for the proposed effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 2007M-0468 and/or RIN number _____ (if a RIN number has been assigned), by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described previously, in the **ADDRESSES** portion of this document under **Electronic Submissions**.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal

information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Erik Mettler, Office of Policy (HF-11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3360, FAX: 301-594-6777, e-mail: erik.mettler@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background and Proposed Amendments

FDA is proposing to amend its regulations regarding changes to an approved NDA, BLA, or PMA to codify the agency's longstanding view on when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review and approval of such change. With respect to drugs, FDA's current regulation, 21 CFR 314.70(c)(6)(iii), provides that certain labeling changes related to an approved drug may be implemented upon receipt by the agency of a supplemental new drug application (sNDA) that includes the change.¹ The corresponding regulation for biologics, 21 CFR 601.12(f)(2), provides that products with certain labeling changes may be distributed before FDA approval. Similarly, with respect to devices, 21 CFR 814.39(d) provides that certain labeling changes may be placed into effect upon submission of a PMA supplement, but prior to the sponsor's receipt of a written FDA order approving the supplement. The supplements described by §§ 314.70(c), 601.12(f)(2), and 814.39(d) are commonly referred to as "changes being effected supplements" or "CBE supplements."² FDA is proposing to amend these provisions to reaffirm that a CBE supplement is

appropriate to amend the labeling for an approved product only to reflect newly acquired information and to clarify that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or medical device.

FDA is the expert public health agency charged by Congress with ensuring that drugs, biologics, and medical devices are safe and effective, and ensuring that the labeling for approved products appropriately informs users of the risks and benefits of the product. Accordingly, the Federal Food, Drug, and Cosmetic Act (the act) requires new drugs, biologics, and certain Class III medical devices to be approved by FDA prior to their distribution in interstate commerce. See 21 U.S.C. 505(a); 42 U.S.C. 262(a)(1); 21 U.S.C. 360e(a). Under these provisions, FDA's review and prior approval of both the product and its proposed labeling is a necessary condition of lawful distribution of the product in interstate commerce.

The CBE supplement procedures set forth in §§ 314.70(c)(6)(iii), 601.12(f)(2), and 814.39(d) must be understood in light of these statutory requirements. Allowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress. Indeed, permitting a sponsor to unilaterally rewrite the labeling for a product following FDA's approval of a product and its labeling would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated. Accordingly, FDA has issued regulations providing that, prior to a sponsor making most labeling changes, it must submit a supplemental application fully explaining the basis for the change and obtain the prior approval by FDA of the supplemental application. See §§ 314.70(b), 601.12(f)(1), 814.39(a)(2).

The CBE supplement procedures are narrow exceptions to this general rule. Although CBE supplements permit sponsors to implement labeling changes before FDA approval of the change, FDA views a CBE supplement as a mechanism primarily designed to provide information to FDA so that the agency can decide when safety information should be included in the labeling for a product. As with prior approval supplements, FDA will carefully review any labeling change proposed in a CBE supplement, as well as the underlying information or data

supporting the change. FDA has the authority to accept, reject, or request modifications to the proposed changes as the agency deems appropriate, and has the authority to bring an enforcement action if the added information makes the labeling false or misleading. See 21 U.S.C. 352(a). For these reasons, as a practical matter, FDA encourages sponsors to consult with FDA prior to adding safety-related information to the labeling for an approved product even when such a change is submitted in a CBE supplement, and sponsors typically do so. The ultimate authority over drug, biologic, and medical device labeling, therefore, continues to rest with FDA.

The history of the CBE procedure supports this narrow understanding of these provisions. The CBE procedure can be traced to a 1965 policy that was based on FDA's enforcement discretion. In 1965, the agency stated that "certain kinds of changes in the labeling and manufacturing of new drugs, proposed in supplemental new drug applications, should be placed into effect at the earliest possible time." (30 FR 993, January 30, 1965). FDA announced, therefore, that agency would "take no action" if a sponsor implemented certain labeling changes "prior to his receipt of a written notice of approval of the supplemental new-drug application," assuming certain conditions were satisfied. (30 FR 993 at 994.)

FDA proposed what is essentially the current CBE procedure in 1982. When proposed, the agency made clear that CBE supplements were intended to apply only if the sponsor became aware of newly discovered safety information that was appropriate for inclusion in the labeling for the product. Indeed, in the preamble to the proposed rule for the CBE provision for drugs, the agency stated: "[S]ome information, although still the subject of a supplement, would no longer require agency preclearance. These supplements would describe changes placed into effect to correct concerns about *newly discovered* risks from the use of the drug." (47 FR 46622, 46623, October 19, 1982) (emphasis added). In that preamble, the agency also emphasized that the CBE procedure was a limited exception to the general requirement of prior FDA approval for a labeling change:

Although most changes in labeling would require the applicant to submit a supplement and obtain FDA approval before making a change, the following changes in labeling, which would make available important new information about the safe use of a drug product, could be made if the applicant submits a supplement when the change is

¹ CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. See 21 CFR 314.50(b)(10); *see also* 57 FR 17950, 17953, and 17961.

² For devices, such supplements are also referred to as Special PMA Supplements. For convenience, this document will use the term CBE supplement.

made: Changes that add or strengthen a contraindication, warning, precaution, or statement about an adverse reaction, drug abuse, dependence, or overdosage, or any other instruction about dosage and administration that is intended to improve the safe use of the product.

(47 FR 46622 at 46635) (emphasis added). Similarly, in the preamble to the final rule, FDA again emphasized that CBE supplements were intended as a narrow exception to the general rule that labeling changes require FDA's prior approval:

Drug labeling serves as the standard under which FDA determines whether a product is safe and effective. Substantive changes in labeling *** are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug. Thus, they are appropriately approved by FDA in advance, unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user.

(50 FR 7452-01, 7470, February 22, 1985).

Recent changes to the act made by the Food and Drug Administration Amendments Act (FDAAA), Public Law 110-85, 121 Stat. 823 (September 27, 2007) confirm that Congress intends FDA to carefully regulate the content of labeling for approved products. Among other provisions, FDAAA provided new authority to FDA to initiate labeling changes for approved drugs and biologics. Under the act as amended, “[i]f the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug,” the agency may trigger a process to rapidly amend the labeling for the product (21 U.S.C. 355(o)(4)(A)). The FDAAA provisions were intended to ensure that FDA-initiated labeling changes would be made quickly in order to respond to new or emerging information about an approved drug or biologic. These provisions provide streamlined authority for FDA to respond to new and emerging safety information.³ FDA believes that its understanding of §§ 314.70(c)(6)(iii) and 601.12(f)(2) as reflected in this document is consistent with this enhanced authority for FDA to control the labeling for drugs and biologics.

In the device context, FDA has previously stated that a CBE supplement

constitutes “a narrow exception to the general rule that prior FDA approval of changes to a PMA, including the labeling for a device, is a condition of lawful distribution.” See Draft Guidance: Modifications to Devices Subject to Premarket Approval (PMA)—The PMA Supplement Decision-Making Process (March 9, 2007) (<http://www.fda.gov/cdrh/ode/guidance/1584.pdf>). “Allowing a manufacturer to add a safety-related warning using a [CBE supplement] based on information that was known to the FDA during the rigorous PMA review process would undermine that important process.” Id. For this reason, a CBE supplement may only be utilized where “the manufacturer has newly acquired safety-related information.” Id. Moreover, “any such change should be considered temporary while FDA reviews the supplement, including the basis for *** how the change enhances the safety of the device or the safety in the use of the device.” Id.

For these reasons, FDA believes it necessary to amend its regulations to make explicit the agency’s understanding that a sponsor may utilize the limited CBE provisions only to reflect newly acquired safety information. FDA intends to consider information “newly acquired” if it consists of data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product. For example, if a postmarket study demonstrates that an approved product has a more severe risk of a significant adverse reaction than previously known, a CBE supplement may be appropriate. However, if a postmarket study provides data about a product that is cumulative of information previously submitted to FDA, a CBE supplement would not be appropriate. Similarly, if a sponsor receives reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, such information may be considered newly acquired information that could form the basis for an appropriate CBE supplement. However, if the reports of adverse events are consistent in type, severity, and frequency with information previously provided to FDA, such reports may not constitute newly acquired information appropriate for a CBE supplement. FDA also intends to consider significant new analyses of

previously submitted data (e.g., meta-analyses) that provide novel information about the product to constitute newly acquired information. FDA invites comments regarding the circumstances when information regarding a safety issue associated with a drug, biologic, or medical device should be considered newly acquired and thus appropriate to be included in a CBE supplement.

Moreover, FDA proposes to clarify that a CBE supplement may be used only to implement labeling changes regarding contraindications,⁴ warnings, precautions, or adverse reactions in circumstances when there is sufficient evidence of a causal association with the drug, biologic, or medical device.

FDA’s regulations regarding the content and format of labeling for prescription drugs and biologics are codified in §§ 201.57 and 201.80 (21 CFR part 201).⁵ Section 201.57(c) provides criteria for when safety information is appropriate for inclusion in the labeling for an approved drug or biologic. With respect to warnings and precautions, a sponsor is obligated to update labeling for an approved product to include “a warning about a *clinically significant hazard* as soon as there is *reasonable evidence of a causal association* with a drug”, even though a causal relationship “need not have been definitely established.” (§ 201.57(c)(6) (emphasis added)). With respect to adverse reactions, the rule requires the listing of adverse reactions that are “reasonably associated with use of a drug” (§ 201.57(c)(7) (emphasis added)). The rule provides that not all adverse events observed during use of a drug are eligible for inclusion in labeling, but rather “only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.” Id. (emphasis added), c.f. § 314.80(e) (sponsor need not submit a 15-day alert report for an adverse drug experience obtained from a

³ As FDA has stated, Federal law governs not only what information must appear in labeling, but also what information may not appear. (71 FR 3922 at 3935, January 24, 2006) (“FDA interprets the act to establish both a ‘floor’ and a ‘ceiling,’ such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading.”)

⁴ Section 201.57 is applicable to recently approved drugs and biologics and certain other products (see also § 201.56) (describing implementation schedule). Older products generally are subject to the labeling requirements set forth in § 201.80.

postmarketing study "unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience"). Similarly, with respect to contraindications, § 201.57 provides that labeling should include situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit. The rule directs that sponsors list only "[k]nown hazards and not theoretical possibilities" as contraindications (§ 201.57(c)(5); see also 71 FR 3922 at 3927) ("FDA believes that including relative or hypothetical hazards [as contraindications] diminishes the usefulness of this section.").

Section 201.80 sets forth similar, although not identical, criteria for the inclusion of safety-related information in the labeling for products subject to that provision. Because § 201.57 represents the agency's most recent consideration of this topic, (see 71 FR 3922), FDA proposes that, if a sponsor intends to utilize the limited CBE procedure set forth in § 314.70(c)(6)(iii) or § 601.12(f), it must possess information regarding causation sufficient to satisfy the criteria set forth in § 201.57(c), regardless of whether the drug or biologic is subject to the labeling requirements of § 201.57 or § 201.80. FDA invites comments on this topic.

Medical devices subject to PMA approval follow similar labeling standards. For example, in 1991 FDA published a memorandum describing the agency's approach to device labeling. See Device Labeling Guidance, General Program Memorandum G91-1 (March 8, 1991) (<http://www.fda.gov/cdrh/g91-1.htm>). In that guidance, the agency stated that the labeling for a medical device should include a warning "if there is reasonable evidence of an association of a serious hazard with the use of the device," even though a causal relationship "need not have been proved." *Id.* at section V (emphasis added). With respect to adverse reactions, the agency advised that labeling should include a listing of adverse reactions that are "reasonably associated with use of a device." *Id.* at section VI (emphasis added). With respect to contraindications, the guidance recommended that labeling include situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Labeling should include only "[k]nown hazards and not theoretical possibilities." *Id.* at section V. For example, if a hypersensitivity to an ingredient in a device has not been demonstrated, it should not be listed as

a contraindication in the labeling. *Id.* Accordingly, FDA proposes that in order to utilize the limited CBE exception, there should be, at minimum, reasonable evidence of a causal association between the device and the warning, precaution, adverse event, or contraindication sought to be added.

Explicitly requiring that CBE supplements are utilized in a manner proposed by this amendment ensures that only scientifically justified information is provided in the labeling for an approved product. Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device or decrease the usefulness and accessibility of important information by diluting or obscuring it. As FDA has stated, labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance. See, e.g., "Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care" (August 1993) (<http://www.fda.gov/cdrh/dsmo/897.pdf>) ("Overwarning has the effect of not warning at all. The reader stops paying attention to excess warnings.") For this reason, sponsors should seek to utilize §§ 314.70(c)(6)(iii)(A), 601(f)(2)(A), and 814.39(d)(2)(i) only in situations when there is sufficient evidence of a causal association between the drug, biologic, or medical device and the information sought to be added. For example, Draft Guidance, Public Availability of Labeling Changes in "Changes Being Effected Supplements" (September 2006) (<http://www.fda.gov/cder/guidance/7113dft.htm>) ("FDA would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event."); *Colocicco v. Apotex Inc.*, No. 06-3107, Br. of United States (3d Cir. filed December 4, 2006) (stating that § 314.70(c)(6)(iii) "does not alter the requirement that any warning must be based on 'reasonable evidence of an association of a serious hazard with a drug.'") (citations omitted)).

Accordingly, FDA is proposing to amend §§ 314.70(c)(6)(iii)(A), 601.12(f)(2)(A), and 814.39(d)(2)(i) to make explicit the agency's view that CBE supplements may be used to strengthen a contraindication, warning, precaution, or adverse reaction only when there is sufficient evidence of a causal association.

These proposed amendments to FDA's CBE regulations are consistent with the agency's role in protecting the

public health. Before approving an NDA, BLA, or PMA, the FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is scientific basis to be included in the FDA-approved labeling. Under the act, the Public Health Service Act (PHS Act), and FDA regulations, the agency makes approval decisions, including the approval of supplemental applications, based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling. See, e.g., 21 U.S.C. 355(d); 42 U.S.C. 262; 21 U.S.C. 360e(d)(2). FDA's comprehensive review is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA's approval of an application is expressly conditioned upon the applicant incorporating the specified labeling changes exactly as directed. For example, §§ 314.105(b), 814.44(d)(1). Moreover, after approval, FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate. Allowing a sponsor, without prior FDA approval, to add information to the labeling for a product based solely on data previously submitted to the FDA would undermine FDA's approval process and could result in unnecessary or confusing information being placed in the labeling for a drug, biologic, or medical device.

For these reasons, FDA is proposing to amend its regulations to make explicit the agency's longstanding position and practice regarding CBE supplements. FDA does not consider this amendment to be a substantive change, and it would not alter the agency's existing practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement.

II. Legal Authority

This rule, if finalized, would amend §§ 314.70, 601.12, and 814.39 in a manner consistent with the agency's current understanding and application of those provisions. FDA's legal authority to modify §§ 314.70, 601.12, and 814.39 arises from the same authority under which FDA initially issued these regulations. Both the act and the PHS Act provide FDA with authority over the labeling for approved

drugs, biologics, and medical devices, and authorizes the agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for such products.

Section 502 of the act (21 U.S.C. 352) provides that a drug, biologic,⁶ or medical device will be considered misbranded if, among other things, the labeling for the product is false or misleading in any particular (21 U.S.C. 352(a)). Under section 502(f) of the act, a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage or methods or duration of administration or application. Moreover, under section 502(j) of the act, a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505 of the act (21 U.S.C. 355), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Similarly, under section 515(d)(2) of the act (21 U.S.C. 360e(d)(2)), FDA must assess whether to approve a PMA according to the "conditions of use prescribed, recommended, or suggested in the proposed labeling" of the device. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Section 351 of the PHS Act (42 U.S.C. 262) provides additional legal authority for the agency to regulate the labeling of biological products. Licenses for biological products are to be issued only upon a showing that the biological product is safe, pure, and potent (42 U.S.C. 262(a)). Section 351(b) of the PHS Act (42 U.S.C. 262(b)) prohibits any person from falsely labeling any package or container of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 as amended, the Regulatory Flexibility Act (5 U.S.C. 601–612), and

the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed amendments to existing regulations are intended only to clarify the agency's interpretation of current policy, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The objective of the proposed rule is to make explicit the agency's longstanding view of when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review of the change. More specifically, the purpose of the proposed rule is to codify the agency's understanding that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information, and to clarify that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the approved product. FDA does not consider this to be a substantive policy change, and it does not alter the agency's current practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement.

Because the proposed rule does not establish any new regulatory or record keeping requirements, the agency does not expect that there will be any associated compliance costs. The proposed rule simply codifies the agency's longstanding interpretation of when sponsors are allowed to add information regarding the risks associated with a product to the labeling without prior approval from FDA. It is expected that the proposed codifications would promote more effective and safe use of approved products. The agency believes that any potential impacts of the proposed rule would be minimal because this action does not represent a substantive policy change.

IV. Paperwork Reduction Act of 1995

This proposed rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The collections of information in: 21 CFR part 314 have been approved under OMB Control No. 0910–0001 (expires May 31, 2008); 21 CFR part 601 have been approved under OMB Control No. 0910–0338 (expires June 30, 2010); and 21 CFR part 814 have been approved under OMB Control No. 0910–0231 (expires November 30, 2010). Therefore, FDA tentatively concludes that the proposed requirements in this document are not subject to review by OMB because they do not constitute a "new collection of information" under the PRA.

V. Environmental Impact

The agency has determined under 21 CFR 25.31(a) and 25.34(e) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Federalism

The agency has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Under the principles of implied conflict preemption, courts

⁶ Although the language of section 502 of the act refers only to drugs and devices, it is also applicable to biologics. (See 42 U.S.C. 262(j)).

have found state law preempted where it is impossible to comply with both federal and state law or where the state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." See *English v. General Electric Co.*, 496 U.S. 72, 79 (1990); *Florida Lime & Avocado Growers, Inc.*, 373 U.S. 132, 142–43 (1963); *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

If finalized as proposed, this rule codifies longstanding agency policy and understanding with respect to §§ 314.70(c)(6)(iii), 601.12(f) and 814.39(d). To the extent that state law would require a sponsor to add information to the labeling for an approved drug or biologic without advance FDA approval based on information or data as to risks that are similar in type or severity to those previously submitted to the FDA, or based on information or data that does not provide sufficient evidence of a causal association with the product, such a state requirement would conflict with federal law. In such a situation, it would be impossible to market a product in compliance with both federal and state law, and the state law would "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines*, 312 U.S. at 67. Moreover, such a state law requirement relating to a medical device would constitute a requirement that is different from, or in addition to, a federal requirement applicable to the device, and which relates to the safety or effectiveness of the device. 21 U.S.C. 360k(a).

FDA believes that the proposed rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that when adjudication or rulemaking could have a preemptive effect on state law, "the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." By publication of this proposed rule, FDA invites comments from State and local officials. FDA also intends to provide separate notice of this proposed rule to the States.

VII. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) written or electronic comments regarding this document. Submit a single copy of electronic comments or three paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the

docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Please note that in January 2008, the FDA Web site is expected to transition to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. After the transition date, electronic submissions will be accepted by FDA through the FDMS only. When the exact date of the transition to FDMS is known, FDA will publish a *Federal Register* notice announcing that date.

VIII. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal be effective on the date of its publication in the *Federal Register*.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 314, 601, and 814 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356a, 356b, 356c, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122 Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

5. Section 601.12 is amended by revising paragraphs (f)(2)(i) introductory text and (f)(2)(i)(A), and by adding paragraph (f)(6) to read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to reflect newly acquired information, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made under paragraph (f)(1) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the

previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (e.g., meta-analyses).

* * * * *

3. Section 314.70 is amended by revising paragraphs (c)(6)(iii) introductory text and (c)(6)(iii)(A) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(c) * * *

(6) * * *

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c) of this chapter;

* * * * *

PART 601—LICENSING

4. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122 Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

5. Section 601.12 is amended by revising paragraphs (f)(2)(i) introductory text and (f)(2)(i)(A), and by adding paragraph (f)(6) to read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to reflect newly acquired information, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made under paragraph (f)(1) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the

evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(5) For purposes of paragraph (f)(2) of this section, information will be considered newly acquired if it consists of data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (e.g., meta-analyses).

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

6. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 360, 360c-360j, 371, 372, 373, 374, 375, 379, 379e, 381.

7. Section 814.3 is amended by adding paragraph (o) to read as follows:

§ 814.3 Definitions.

(o) *Newly acquired information* means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (e.g., meta-analyses).

8. Section 814.39 is amended by revising paragraphs (d)(1) introductory text and (d)(2)(i) to read as follows:

§ 814.39 PMA supplements.

(d)(1) After FDA approves a PMA, any change described in paragraph (d)(2) of this section to reflect newly acquired information that enhances the safety of the device or the safety in the use of the device may be placed into effect by the applicant prior to the receipt under § 814.17 of a written FDA order approving the PMA supplement provided that:

(2) * * *

(i) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction for which there is reasonable evidence of a causal association.

* * * *

Dated: December 4, 2007.

Jeffrey Shuren,
Assistant Commissioner for Policy.
(FR Doc. E8-702 Filed 1-15-08; 8:45 am)
BILLING CODE 4160-01-S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 704, 720, 721, and 723

(EPA-HQ-OPPT-2007-0392; FRL-8131-8)

RIN 2070-AJ21

Proposed Clarification for Chemical Identification Describing Activated Phosphors for TSCA Inventory Purposes

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed clarification.

SUMMARY: This document proposes a clarification under which activated phosphors that are not on the Toxic Substances Control Act (TSCA) section 8(b) Chemical Substance Inventory (TSCA Inventory) would be considered to be new chemical substances under TSCA section 5, thus would be subject to the notification requirements under TSCA section 5(a) new chemical notification requirements. In certain letters and other interpretations issued by EPA from 1978 to 2003, it appears that the Agency erroneously indicated that activated phosphors constitute solid mixtures for purposes of the TSCA Inventory, and thus that they were not separately reportable as chemical substances under TSCA section 5(a) new chemical notification requirements. This proposed clarification is necessary because EPA's interpretations in this area have not been consistent. Given this past inconsistency, EPA is seeking comment on its proposed clarification.

DATES: Comments must be received on or before March 17, 2008.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA-HQ-OPPT-2007-0392, by one of the following methods:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the on-line instructions for submitting comments.

- *Mail:* Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.

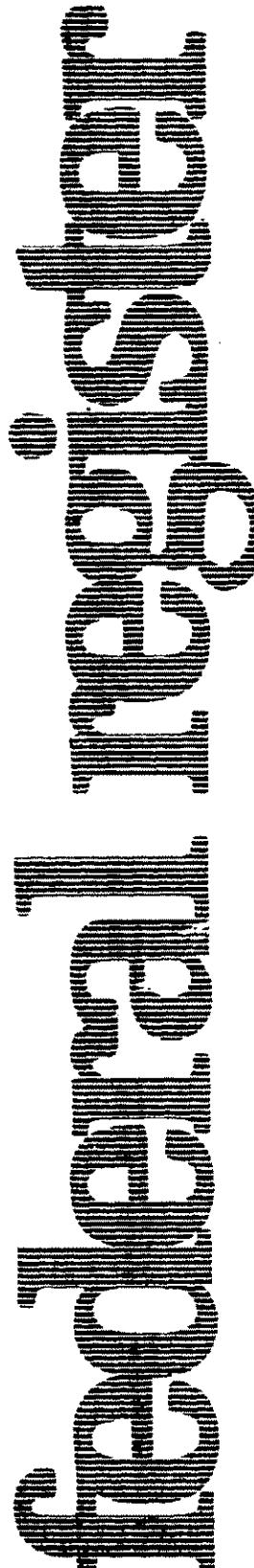
- *Hand Delivery:* OPPT Document Control Office (DCO), EPA East Bldg., Rm. 6428, 1201 Constitution Ave., NW., Washington, DC. Attention: Docket ID

Number EPA-HQ-OPPT-2007-0392. The DCO is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the DCO is (202) 564-8930. Such deliveries are only accepted during the DCO's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to docket ID number EPA-HQ-OPPT-2007-0392. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at <http://www.regulations.gov>, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov website is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses. For additional information about EPA's public docket, visit the EPA Docket Center homepage at <http://www.epa.gov/epohome/dockets.htm>.

Docket: All documents in the docket are listed in the docket index available in regulations.gov. To access the electronic docket, go to <http://www.regulations.gov>, select "Advanced Search," then "Docket Search." Insert the docket ID number where indicated and select the "Submit" button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket

EXHIBIT B



Tuesday,
April 28, 1992

Part II

**Department of
Health and Human
Services**

Food and Drug Administration

**21 CFR Parts 2, et al.
Abbreviated New Drug Regulations; Final
Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

21 CFR Parts 2, 5, 10, 310, 314, 320, and 433

[Docket No. 85N-0214]

RIN 0905-AB63

Abbreviated New Drug Application Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations for most of its requirements for abbreviated new drug applications (ANDA's). FDA published a proposed rule for ANDA's in the Federal Register of July 10, 1989 (54 FR 28872). These regulations implement title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments). This final rule covers subjects such as ANDA content and format, approval and nonapproval of an application, and suitability petitions. This rule does not finalize the provisions of the proposed rule on patent certification and market exclusivity; FDA is still examining the issues pertaining to those provisions and will finalize them in a future edition of the Federal Register.

EFFECTIVE DATE: The regulations will become effective on June 29, 1992.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Center for Drug Evaluation and Research (HFD-382), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

SUPPLEMENTARY INFORMATION:

I. Background

A. New Drug Approval: 1938 to 1982

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the act). The act created a premarket approval system for drug products that required applicants seeking drug product approval to submit a new drug application (NDA) to FDA. The NDA would contain information demonstrating, among other things, that the drug product was safe. The act also provided that an NDA would automatically become effective (i.e., the product could be lawfully marketed) within a fixed period unless the agency affirmatively refused to approve the application.

In addition to drug products that had an effective NDA, many products were

marketed without effective applications. These products were identical, similar, or related to products with effective NDA's. The manufacturers of these products had concluded that their drug products were generally recognized as safe, or had received advisory opinions from FDA that an NDA was not required because the products were generally recognized as safe.

In 1962, Congress amended the drug approval provisions of the act to require affirmative approval to NDA's before marketing. The amendments required applicants to show that their products were both safe and effective (Pub. L. 87-781 (October 10, 1962)). Thus, on or after October 10, 1962, a person could not market a new drug without an approved NDA that contained sufficient safety information as well as substantial evidence establishing the drug's effectiveness for its intended uses.

The 1962 amendments also deemed NDA's that had become effective before October 10, 1962, to be approved. As with postenactment drugs, the 1962 amendments required these "pre-1962" drugs to be shown to be effective for their intended uses. Consequently, FDA began a program to evaluate the drugs that had been deemed approved to determine whether there was substantial evidence of their effectiveness. This systematic evaluation and the implementation of FDA's findings became known as the Drug Efficacy Study Implementation (DESI). Under DESI, FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC), which established expert panels to review available evidence of effectiveness and to provide recommendations to FDA. FDA considered the NAS/NRC panels' recommendations about the effectiveness of these DESI drugs, and announced its conclusions through Federal Register notices. These notices, known as DESI notices, contain the acceptable marketing conditions for the class of drug products covered by the notice.

B. The ANDA Procedure for Pre-1962 Drugs

If a manufacturer had a pre-1962 NDA in effect for a drug product, FDA continued its approval if the manufacturer submitted a supplemental new drug application to conform the product's indications for use to those determined to be effective in the DESI review. Yet, as stated above, many drug products had active ingredients and indications that were identical or very similar to the drug products found to be effective in the DESI review but lacked

NDA's themselves. In implementing the DESI program with respect to these duplicate products, FDA concluded that each such drug product was a "new drug" that required its own approved NDA before it could be legally marketed (*United States v. Generix Drug Corp.*, 460 U.S. 453 (1983)). Additionally, FDA issued a policy statement in the Federal Register of May 28, 1968 (33 FR 7758) that revoked the earlier advisory opinions that drugs could be marketed without prior FDA clearance. This rule was codified at 21 CFR 310.100.

Shortly thereafter, FDA created the ANDA procedure for the approval of duplicate products in reliance on the DESI evaluation. In brief, after the DESI program had found a particular drug product to be effective and suitable for ANDA's, FDA published a Federal Register notice announcing its conclusions. Any manufacturer of a duplicate drug product that did not have an approved NDA was then required to submit an ANDA to obtain approval to market the duplicate version of the approved drug. (See 34 FR 2673, February 27, 1969; 35 FR 6574, April 24, 1970; and 35 FR 11273, July 14, 1970.)

Before 1984, FDA based these ANDA approvals on the theory that the evidence of effectiveness necessary for approval of an NDA had been provided, reviewed, and accepted during the DESI process. Evidence of the drug's safety had been determined on the basis of information contained in the pioneer NDA and by the subsequent marketing experience with the drug. FDA required ANDA applicants to submit information that showed the applicant's ability to manufacture a product of acceptable quality whose safety and effectiveness were equivalent to the drug product whose safety and effectiveness had been established. Thus, ANDA applicants provided information on the drug product's formulation, manufacture, quality control procedures, and labeling. DESI notices specified additional information, such as bioavailability/bioequivalence data, for the ANDA.

C. Procedures for Duplicates of Post-1962 Drugs ("Pioneer NDA" Policy)

FDA never extended its ANDA policy for pre-1962 drugs to duplicates of drugs first approved for marketing on or after October 10, 1962, although it did consider the possibility of such an extension either by regulation or through legislation. (See 54 FR 28872 at 28873 and citations therein.) As patents began to expire for many post-1962 drugs, including some high volume, therapeutically important drug products,

many manufacturers became interested in changing the NDA system to permit ANDA's for post-1962 drug products.

FDA did allow some duplicats drug products of drugs first approved after 1962 to be marketed under its "paper NDA" policy. (See 46 FR 27398, May 19, 1981.) This policy permitted FDA to approve NDA's for post-1962 drug products on the basis of safety and effectiveness information derived primarily from published reports based on well-controlled studies. This meant that manufacturers did not have to conduct their own tests, but adequate literature, including detailed reports of adequate and well-controlled studies, was available for only a fraction of the post-1962 drugs. Moreover, the staff effort involved in reviewing paper NDA's ultimately proved to be a substantial and inefficient use of agency resources.

D. The Drug Price Competition and Patent Term Restoration Act of 1984

From 1978 to 1984, Congress considered various bills that would have authorized an ANDA procedure for duplicate versions of post-1962 drug products. Other bills under consideration during this period sought to restore patent life lost while awaiting Federal marketing approval. Congress combined the ANDA procedure for post-1962 drug products and patent term restoration in the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417).

The law consisted of two different titles. Title I authorized the approval of duplicate versions of drug products, approved under section 505 of the act, under an ANDA procedure. Title II authorized the extension of patent terms for approved new drug products (including antibiotics and biological drug products), some medical devices, food additives, and color additives. Congress intended the two titles to provide a careful balance between promoting competition among brand-name and duplicate or "generic" drugs and encouraging research and innovation.

Title I amended section 505 of the act by establishing a statutory ANDA procedure for duplicate and related versions of human drugs approved under section 505(b) of the act. These procedures are inapplicable to antibiotics (which are approved under section 507 of the act) and biological drug products licensed under 42 U.S.C. 262. The statute adopted, with few modifications, the agency's ANDA procedure for pre-1962 drugs. It required all applicants to provide certain patent information; provided for the submission

and approval of applications for which the investigations relied on by the applicant to satisfy the "full reports" of safety and effectiveness requirement were not conducted by or for which the applicant had not obtained a right of reference or use from the person who conducted the investigations; established rules for disclosure of safety and effectiveness data submitted as part of an NDA; and provided specific time periods during which ANDA's and NDA's for certain drug products may not be submitted or approved. The act also required FDA to promulgate new regulations implementing the statute. In the Federal Register of July 10, 1989 (54 FR 28872), FDA published a proposed rule on ANDA's. This final rule contains most of the provisions contained in that proposal.

FDA published a final rule implementing Title II in the Federal Register of March 7, 1988 (53 FR 7298). This rule is codified at 21 CFR Part 60.

II. Highlights of this Final Rule

This final rule amends 21 CFR Part 314 to establish new requirements and procedures for NDA and ANDA applicants under the 1984 amendments. The rule also revises the bioavailability and bioequivalence requirements at 21 CFR part 320 to conform to the 1984 amendments and current agency policy. Minor conforming amendments are made to 21 CFR parts 2, 5, 10, 310, 314, and 433. Additionally, because the agency will issue final regulations governing patent certification and marketing exclusivity requirements at a future date, FDA has revised or deleted cross-references to those provisions and, where possible, replaced them with statutory citations.

The final rule's major provisions are as follows:

A. Abbreviated Applications

The statutory provisions governing ANDA requirements and procedures are at section 505(j) of the act (21 U.S.C. 355(j)).

The statute permits ANDA's for: (1) A drug product that is the "same" as a drug product listed in the approved drug product list published by FDA (the "listed drug") with respect to active ingredient(s), route of administration, dosage form, strength, and conditions of use recommended in the labeling; and (2) a drug product with certain changes from a listed drug if FDA has approved a petition from a prospective applicant permitting the submission of an ANDA for the changed drug product.

Subpart C of part 314 addresses an ANDA applicant's requirements and responsibilities. The final rule is

substantially similar to the proposal, although FDA has made some minor changes, such as requiring applicants to include a table of contents in the review copies of an ANDA (21 CFR 314.94(a)(2)), and other minor changes regarding periodic reports from ANDA holders (21 CFR 314.98). One noteworthy change concerns the chemistry, manufacturing, and controls section of an ANDA. Under the proposed rule, applicants would have been required to identify and characterize inactive ingredient differences between their products and those in the reference listed drug. FDA received numerous comments stating that, for many drug products, applicants would be unable to discover which inactive ingredients were used in the reference listed drug. Consequently, the final rule requires applicants to identify and describe such differences regarding inactive ingredients only for topical drug products, drug products intended for parenteral use, and drug products intended for ophthalmic or otic use. The inactive ingredients for these products are listed on the products' labels. For other drug products, the final rule requires applicants to identify and characterize only the inactive ingredients in their own products.

FDA has also revised some policies that were announced in the preamble to the proposed rule. For example, the preamble to the proposed rule indicated that FDA would accept an ANDA submission that contained a bioequivalence protocol. This policy had the unintended effect of encouraging applicants to file incomplete ANDA's. Therefore, FDA is announcing that it will no longer accept an ANDA that does not contain the results of a complete bioequivalence study if such a study is required for approval. These and other changes are described in more detail in the responses to comments below.

B. ANDA Suitability Petitions

Under section 505(j)(2)(C) of the act, an ANDA applicant may petition FDA for permission to file an ANDA for a drug product that has one different active ingredient in a combination product, or whose route of administration, dosage form, or strength differs from that of the listed drug. These are the only types of changes permitted in an ANDA.

The final rule, at 21 CFR 314.93, describes the information that a petitioner must include in its petition. The information must demonstrate that the changes from the listed drug requested for the proposed drug product

may be adequately evaluated for approval without data from investigations to show the proposed drug product's safety or effectiveness and that a drug product with a different active ingredient may be adequately evaluated for approval as safe and effective on the basis of information required to be submitted in an ANDA.

In the preamble to the 1989 proposed rule, FDA invited comments on a policy that would provide for the confidentiality of any petition submitted under section 505(j)(2)(C) of the act until FDA either approved or disapproved the petition. At the time of the proposed rule, FDA's policy was to make these petitions available to the public. The agency received an equal number of comments in favor of and opposed to such a policy. The comments favoring confidentiality argued that the public availability of suitability petitions would adversely affect the petitioner's commercial interests. The comments opposing confidentiality said that the public availability of these petitions would enhance the decisionmaking process. FDA agrees with the latter view. By making suitability petitions publicly available, FDA has received valuable comments and information from third parties. These comments and information have contributed to the agency's evaluation of some suitability petitions. Consequently, FDA will continue its policy of making such petitions available to the public.

An ANDA submitted under an approved petition would generally be required to contain the same information as an ANDA for a drug product that is the same as a listed drug except that FDA may require additional information regarding the difference between the proposed drug product and the listed drug. Additionally, FDA requires that the listed drug referred to in the ANDA be the one upon which the petition was based and that the applicant refer to the petition in its ANDA and include a copy of FDA's response approving submission of an ANDA.

C. 505(b)(2) Applications

The 1984 amendments also amended section 505(b) of the act (21 U.S.C. 355(b)) to create another type of application. These applications, known as 505(b)(2) applications, are similar to applications under the agency's "paper NDA" policy. Unlike the paper NDA policy, however, section 505(b)(2) of the act applies to applications that contain investigations relied upon by the applicant to provide full reports of safety and effectiveness where the investigations were not conducted by or

for the applicant and the applicant has not obtained a right of reference or use from the person who conducted the investigations. (See 21 U.S.C. 355(j)(2).) Thus, section 505(b)(2) of the act is not restricted to literature-supported NDA's for duplicates of approved drugs; it covers all NDA's for drug products that rely on studies not conducted by or for the applicant or for which the applicant does not have a right of reference.

A 505(b)(2) application is submitted under section 505(b)(1) of the act. Consequently, these applications are subject to the same statutory provisions as full NDA's. The statute, however, gives 505(b)(2) applicants additional obligations, such as patent certification, that are similar to those of ANDA applicants. The final rule addresses 505(b)(2) application procedures at 21 CFR 314.50.

The preamble to the proposed rule (54 FR 28872 at 28891) asked whether FDA should adopt a policy whereby a 505(b)(2) application for a drug product with a change in dosage form, strength, route of administration, or active ingredient would be treated as a petition under section 505(j)(2)(C) of the act. Most commenters opposed such a policy, asserting that the policies and procedures for 505(b)(2) applications are or should be distinct from those for suitability petitions. After careful consideration, the agency believes that the policy would prolong review of 505(b)(2) applications and suitability petitions. Consequently, FDA will not adopt the proposed policy.

D. Withdrawal or Suspension of Approval of an ANDA

The statute authorizes the Secretary of Health and Human Services (the Secretary) to withdraw or suspend the approval of any ANDA for a generic drug if: (1) Grounds exist for withdrawal under section 505(e) of the act; (2) the approval of the listed drug referred to by the generic applicant is withdrawn or suspended; or (3) the manufacturer voluntarily withdraws the listed drug from sale for what the agency determines are safety or effectiveness reasons. The final rule contains provisions on withdrawal and suspension at 21 CFR 314.150 to 314.153.

III. Comments on the Proposed Rule

Section 10.30—Citizen Petition

Proposed § 10.30 (e)(2) and (e)(4) would have amended FDA's citizen petition regulations to provide for responses to petitions filed in accordance with section 505(j)(2)(C) of the act.

1. FDA received one comment on proposed § 10.30(e)(2). The comment agreed with the provision, and FDA has finalized it without change.

Section 10.45—Court Review of Final Administrative Action; Exhaustion of Administrative Remedies

2. Two comments objected to proposed § 10.45(d), which would make FDA's response to a petition for reconsideration, rather than a response to a petition under section 505(j)(2)(C) of the act, final agency action. Both comments said that FDA had no authority to require a petition for reconsideration and would give petitioners the right to request a hearing or declare FDA's response to the suitability petition to be final agency action.

FDA disagrees with the comments. FDA has the authority to require adherence to a petition for reconsideration procedure, and such a requirement is practical in this case. From a practical standpoint, the agency receives a large number of suitability petitions each year. If every response to a suitability petition were to be considered as final agency action, the agency would be obliged to devote more resources to each petition to create a comprehensive administrative record. This approach would prolong the review of all suitability petitions without any appreciable benefit to petitioners or the agency. In fact, requiring a petition for reconsideration is to the petitioner's benefit because it ensures that senior FDA officials review the decision on the suitability petition. As for the authority to require a petition for reconsideration, the agency does not agree that it lacks authority to establish by regulation what constitutes final agency action on a petition.

Section 310.305—Records and Reports Concerning Adverse Drug Experiences on Marketed Prescription Drugs for Human Use Without Approved New Drug Applications

3. FDA received one comment on proposed § 310.305 (a)(3) and (c)(4), which, in part, would require persons to report or review reports of therapeutic failure. The proposed rule would amend the existing regulation, which required manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved NDA or ANDA to maintain records and report to FDA "(1) all serious, unexpected adverse drug experiences associated with the use of their drug products and (2) any significant increase in the frequency of a serious, expected

adversa drug experience." The comment suggested that FDA delete "therapeutic failure" and replace it with "significant failure of expected pharmacological action."

The agency declines to adopt the comment's suggestion. Section 310.305 uses the term "therapeutic failure" to correspond to similar language for adverse drug experience reporting for drugs subject to premarket approval. (See § 314.80; 54 FR 28872 at 28911.) In the preamble to the proposed rule, FDA explained that it was deleting the word "significant" from the phrase "any significant failure of expected pharmacological action" because the word "significant" had been a source of confusion and ambiguity. (See 54 FR 28872 at 28889.) Thus, FDA proposed to amend §§ 314.80 and 310.305 to require reports of "therapeutic failure" to eliminate this confusion and require all reports of therapeutic failure (54 FR 28872 at 28889).

Section 314.1—Scope

4. FDA received no comments on the proposed changes to 21 CFR 314.1, but did receive two general comments regarding the proposed rule's scope. One comment asked FDA to permit ANDA's for duplicates of "drug substances for which the specifications are very tightly drawn for both potency and purity," such as insulin preparations, and for copies of biotechnology-derived drug products. The second comment recommended that FDA accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label, provided that such information was not indicative of diminished safety or effectiveness of the generic drug product.

Section 505(j) of the act permits ANDA's only for duplicate and related versions of previously approved drug products. The ANDA applicant relies on a prior agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted. Thus, under the statute, an ANDA would only be permitted for a drug product with "tight specifications" or a biotechnology-derived drug product only if such a product is the same as a product previously approved under section 505 of the act or if FDA has approved submission of an ANDA under a petition filed under section 505(j)(2)(C) of the act.

As for accepting ANDA's with additional warnings or precautions, section 505(j)(2)(A)(v) and (j)(3)(G) of the act requires that the applicant's

proposed labeling be the same as that of the reference listed drug unless: (1) The labeling differences are due to an approved petition under section 505(j)(2)(C) of the act (otherwise referred to as a "suitability petition"); or (2) the drug product and the reference listed drug are produced or distributed by different manufacturers. (See 21 U.S.C. 355(j)(2)(A)(v) and (j)(3)(G).) Thus, the exceptions in section 505(j)(2)(A)(v) and (j)(3)(G) of the act are limited. In addition, under the patent and exclusivity provisions of the act, the ANDA labeling may be required to carry fewer indications than the reference listed product's labeling or to have other labeling differences. In the preamble to the proposed rule, the agency described various types of labeling differences that might fall within the permitted exceptions. An ANDA applicant is required to include in its ANDA a side-by-side comparison of the applicant's proposed labeling with the currently approved labeling for the reference listed drug. The agency will carefully review all differences annotated by the applicant in determining if such differences fall within the limited exceptions permitted by the act.

Section 314.3—Definitions

FDA received 14 comments concerning the definitions of "listed drug" and "reference listed drug" under proposed § 314.3. The proposed rule had defined a "listed drug," in part, as:

• a new drug product that has been approved for safety and effectiveness under section 505(c) or approved under section 505(l) of the act, the approval of which has been withdrawn or suspended under section 505(e)(1) through (5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's inclusion in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement to the list.

The proposed rule defined a "reference listed drug" as "the listed drug identified in an abbreviated new drug application or identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application."

With respect to the "listed drug" definition, one comment objected to the exclusion of drugs marketed in compliance with an over-the-counter (OTC) monograph and products with OTC and prescription indications. A second comment said that FDA must list DESI products and post-1962 approved drug products even if the drug products were no longer marketed by September

24, 1984, because section 505(j)(8)(A)(i) of the act requires those products be listed. Four comments objected to listing drugs that have delayed effective dates of approval, while one comment favored listing such drugs.

FDA agrees in part and disagrees in part with the comments. As defined in section 505(j)(8) of the act, a listed drug is one that was approved for safety and effectiveness under section 505(c) of the act or approved under section 505(l) of the act. Drug products marketed in compliance with an OTC monograph rather than pursuant to an approval under section 505(c) or (l) of the act are not listed drugs under the statute.

With respect to DESI products and post-1962 approved drug products that are no longer marketed, FDA stated its position in the preamble to the proposed rule. In brief, FDA declines to allocate its scarce resources to publish and maintain lists of drug products that no longer generate interest with respect to marketing (54 FR 28877 through 28878). FDA does, however, maintain a list of discontinued products as an appendix to the list, and has created a procedure to return these products and other discontinued products to the list where appropriate. If a drug firm wishes to submit an ANDA for a generic version of one of these drug products, it may petition FDA to relist the drug product and provide information to show that the drug product was not withdrawn from sale due to safety or effectiveness reasons.

With respect to drug products with delayed effective dates of approval, FDA has determined that such products should not be listed. An approval with a delayed effective date is tentative and does not become final until the effective date. FDA has concluded that only drug products with final, effective approvals are to be listed under section 505(j)(8) of the act. FDA has amended the definitions of "listed drug" and "the list" to clarify that only drugs with an effective approval are listed drugs.

Similarly, with respect to drug products that are subject to the DESI program and do not meet the conditions for approval of effectiveness as set forth in a DESI notice, FDA has reexamined its policy and no longer regards the DESI notice published in the Federal Register as a "listed drug." Section 505(j)(6) of the act describes a "listed drug" as a drug that has been approved for safety and effectiveness. A drug product that must satisfy the conditions for approval of effectiveness as set forth in a DESI notice, therefore, does not fall within section 505(j)(8) of the act and cannot be a listed drug. Therefore, the

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agency has revised the definition of listed drug so that a DESI notice will not suffice as a "listed drug."

6. Five comments addressed the definition of "reference listed drug." Three comments suggested that the oldest or first NDA product be the reference listed drug while one comment suggested that any FDA-approved drug be a "referenced listed drug." Another comment recommended designating "reference listed drugs" in the publication titled, "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book."

As noted in the preamble to the proposed rule, FDA intends the reference listed drug to be the same drug product selected by the agency as the reference standard for bioequivalence determinations. Therefore, FDA has revised the definition of "reference listed drug" to make clear that a "reference listed drug" is a listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application. In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug. FDA will identify in future editions of the Orange Book those approved drugs that FDA regards as reference listed drugs. In the interim, FDA will maintain a list of reference listed drugs at the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1-23, 12420 Parklawn Dr., Rockville, MD 20857, until the Orange Book can be revised. FDA hopes that designating a single reference listed drug against which all generic versions must be shown to be bioequivalent will avoid possible significant variations among generic drugs and their brand name counterparts. Such variation could result if generic drugs established bioequivalence to different reference listed drugs.

7. One comment recommended defining "appropriate reliance" for purposes of section 505(b)(2) applications. The comment noted that the preamble to the proposed rule had stated "Appropriate reliance on an analysis of (spontaneous) adverse reaction reports will not cause application to be one described by section 505(b)(2) or 505(c)(3)(D) of the

act." (54 FR 28872 at 28891). The comment said it did not believe that an application containing an analysis of adverse reaction reports in place of safety studies "should be considered a full application for the purpose of 'breaking exclusivity' granted to another sponsor's drug."

FDA believes that the comment has misinterpreted the agency's position. The preamble to the proposed rule stated that, for drug products with a U.S. marketing history, an analysis of the spontaneous adverse reaction reports "may, in some cases, be substituted for some of the safety data" in a full NDA (54 FR 28872 at 28891). The agency believes that an analysis of spontaneous adverse reaction can provide some safety information when: (1) The drug product has a U.S. marketing history; and (2) there is a substantial amount of adverse drug reaction experience for that drug product. For example, an applicant could submit such an analysis to substitute for certain animal studies that would otherwise be required to show the kinds of risks that might be expected when the drug is tested in humans, or to show which certain, infrequent side effects occur rather than conduct large, Phase 3 clinical studies to prove the same result. Thus, FDA does not contemplate that an applicant under section 505(b)(1) of the act will substitute an analysis of adverse reaction reports for all safety information.

Section 314.50—Content and Format of an Application

The proposed rule contained several revisions and additions to the existing requirements at 21 CFR 314.50. The proposed revisions were minor. For example, under proposed § 314.50(a)(2), an applicant would be required to provide a statement whether the submission is an original application, a 505(b)(2) application, a resubmission, or a supplement to an application. The proposed additions focused on patent information and certifications and claimed exclusivity, and are not included in this final rule.

8. Proposed § 314.50(g)(3) would require an applicant who is submitting an application under section 505(b) of the act and who has a "right of reference or use" as defined in § 314.4(b) to include a "written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its application, and provide FDA access to the underlying raw data that provide the basis for the report of the investigation submitted in its application." One comment would provide FDA access to

the underlying raw data "only if FDA would not otherwise have access to the information that is needed for an adequate review of the application."

Section 314.50(g)(3) simplifies the process in which FDA can have access to raw data if such data are needed to review an application. Without this provision, if FDA determined that it needed to examine the raw data, it would be obligated to suspend the review process, request that the applicant obtain a written statement from the owner of the data to give FDA access to the data, and wait for the written statement to arrive before continuing its review. The provision, therefore, streamlines the review process by eliminating the need for requests and correspondence between FDA, applicants, and owners of data referenced by applicants after FDA had begun its review. The agency will utilize this authority when it believes that access to the raw data is necessary for reviewing the application.

Section 314.54—Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change from, a Listed Drug

FDA received two comments on proposed § 314.54. This provision would permit any person seeking approval of a drug product that represents a modification of a listed drug and for which investigations other than bioequivalence or bioavailability studies are essential to the approval of the change to submit a 505(b)(2) application.

9. One comment said FDA should revise proposed § 314.54(a) to state that a 505(b)(2) application is appropriate for changing a drug from prescription to OTC status.

FDA declines to adopt the comment. The regulation, as written, does not preclude submission of a 505(b)(2) application to change a drug from prescription to OTC status, so the suggested revision is unnecessary.

10. A second comment objected to proposed § 314.54(b) because it would prevent applicants from submitting applications requiring investigations for approval of a change from a listed drug for drugs whose only difference from the reference listed drug is that the extent to which the listed ingredients are absorbed or otherwise made available to the site of action to a lesser degree compared to the reference listed drug. The comment said FDA should judge drug products individually.

FDA declines to accept the comment. Differences in the extent to which a drug is absorbed will affect the drug's

therapeutic effectiveness. For example, a drug whose extent of absorption is less than that of the reference listed drug may be less effective or even ineffective. Consequently, FDA will not accept applications for products under § 314.54(b) whose extent of absorption is less than that for the reference listed drug.

FDA has, however, amended § 314.54(b) to state that it also will not accept an application under § 314.54 for a product whose only difference from the reference listed drug is an unintentional, lesser rate of absorption. FDA is making this change because a drug whose rate of absorption is unintentionally less than that of the reference listed drug may be less effective.

Section 314.55—Abbreviated Application; Section 314.55—Drug Products for Which Abbreviated Applications are Suitable

FDA received no comments on its proposal to remove these provisions, and, therefore, has removed them from 21 CFR part 314.

Section 314.60—Amendments to an Unapproved Application

11. FDA received two comments on proposed § 314.60. In general, proposed § 314.60 stated when an applicant could submit an amendment to an application filed under § 314.100 but not yet approved, and also stated when an unapproved application could not be amended. One comment asked FDA to explain how exclusivity would be effected if a section 505(b)(2) application is amended before another section 505(b)(2) application, which had been filed earlier, is approved. The second comment claimed that § 314.60(d) would permit section 505(b)(2) applications to become effective regardless of new drug exclusivity. This comment said FDA should revise the rule to declare that a section 505(b)(2) application "that would not be approvable but for a previously approved application *** be made subject to the exclusivity of that previously approved application."

The preamble to the proposed rule explained that, for concurrently pending 505(b)(2) applications, any 505(b)(2) application submitted to FDA before the approval of another NDA that qualifies for exclusivity under section 505(c)(3)(D)(ii) of the act (granting 5 years of exclusivity) is "not affected by this exclusivity provision." (54 FR 28872 at 28901.) This is because section 505(c)(3)(D)(ii) of the act prohibits only the "submission," and not the approval, of a 505(b)(2) application that refers to a previously approved application. Tha

only exception to the policy on concurrently pending 505(b)(2) applications is where "the first applicant to obtain approval and to qualify for exclusivity publishes its data and the competing applicant amends its application to include the first applicant's published data ***. Where that data would be essential to the approval of the competing application, the second application will be deemed to refer to the first application" and not permitted to avoid exclusivity. Id. This policy is covered under § 314.60(b)(1)(ii), so the comment's suggestion is unnecessary.

FDA disagrees with the second comment's assertion that the rule permits section 505(b)(2) applications to become effective regardless of exclusivity. The statute clearly states that the Secretary may not approve, or, in one case, that applicants cannot submit, an application before an exclusivity period expires. (See 21 U.S.C. 355(c)(3)(D)(i) through (c)(3)(D)(v).) The rule observes these restrictions and pertains only to amendments to unapproved applications; it does not address approvals. Section 314.60(b) is, in fact, designed to protect an applicant's exclusivity under section 505(c)(3)(D)(ii) of the act while simultaneously preserving an applicant's incentive to publish the studies on which approval was based. Thus, FDA does not adopt the comment's suggested language.

Section 314.70—Supplements and Other Changes to an Approved Application

FDA received no comments on this provision, but has amended the provision to adopt references to statutory, rather than regulatory, provisions or to explain what information should be provided. However, the agency wishes to remind ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug.

Section 314.71—Procedures for Submission of a Supplement to an Approved Application

FDA received no comments on this provision and has finalized it without change.

Section 314.80—Postmarketing Reporting of Adverse Drug Experiences

FDA proposed several changes to 21 CFR 314.80 under the proposed rule. Section 314.60(a) under the existing regulation defined an "adverse drug experience," in part, as "any significant failure of expected pharmacological

action." The proposed rule would delete the adjective "significant" from this definition and, as a result, require reporting of "any failure of expected pharmacological action." The proposed rule also would require applicants to review all adverse drug experience information "obtained or otherwise received by the application from any source, foreign or domestic," and to review periodically the frequency of reports of adverse drug experiences "that are both serious and expected and reports of therapeutic failure (lack of effect), regardless of source, and report any significant increase in frequency as soon as possible ***."

12. FDA received several comments on adverse drug experience reporting under proposed § 314.80. Four comments supported the rule. Five objected to deleting the adjective "significant" from the phrase "any significant failure of expected pharmacological action" in the existing definition of "adverse drug experience," or asked FDA to limit the rule. The comments said the rule would require additional reports and generate reports with little value.

As stated in the preamble to the proposed rule, FDA deleted the word "significant" from § 314.80 because the word has been a source of confusion and ambiguity (54 FR 28872 at 28889). By amending the rule, FDA intended to require reports of any drug failure, as the agency considers all such failures to be significant. Id. This modification will provide a complete picture of adverse drug experiences, rather than selected reports, and will improve the agency's ability to determine whether it should take regulatory action.

13. One comment said a "therapeutic failure" should include excessive or exaggerated responses to a drug.

FDA declines to amend the rule as suggested. FDA does not consider such responses to be "therapeutic failures" under § 314.80. They are, however, covered under § 314.80 because they usually manifest themselves as adverse drug experiences. Consequently, applicants are obligated to report them as adverse drug experiences.

Section 314.81—Other Postmarketing Reports

The proposed rule would amend 21 CFR 314.81 to require applicants to submit a Form FDA 2657 (Drug Product Listing) within 15 working days of the withdrawal from sale of a drug product. The proposed rule also contained details regarding the information to be submitted, such as the National Drug Code number, the drug product's

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established name and proprietary name, and the date of withdrawal from sale.

14. One comment asked FDA to clarify whether an applicant's obligation to submit postmarketing reports begins when FDA approves its ANDA or when the ANDA approval becomes effective.

Although the preamble to the proposed rule said proposed § 314.81 would apply upon ANDA approval regardless of the ANDA's effective date (54 FR 28872 at 28889), PDA has reconsidered this position in light of its policy on delayed effective dates and approvals. FDA does not consider a drug to be approved until the effective date of approval and regards those drug products with delayed effective dates as having tentative approvals. This policy affects § 314.81 because section 505(k) of the act authorizes reporting requirements for drug products that have an approval "in effect." Thus, an applicant's obligation to submit postmarketing reports will begin when the ANDA approval becomes effective.

15. Two comments addressed the 15-day reporting deadline in proposed § 314.81(b)(3)(iii)(c). One comment said a company "does not always know within 15 days of its last shipment that it intends to discontinue marketing a product" and "it is not always clear to a company whether a product is going to be withdrawn from marketing or just temporarily suspended." The comment would have applicants notify FDA that they will withdraw a product when they decide to permanently withdraw the product from sale. The second comment added that the existing rule's annual reporting requirement was satisfactory.

FDA believes the first comment misinterprets the provision. FDA does not expect parties to submit reports within 15 days from the date of their last shipment. The 15-day period begins from the time the firm decides to withdraw the product from the market. Such withdrawals are not limited to permanent withdrawals; FDA is interested in any decision to discontinue marketing because of the possible implications for the product's safety and efficacy. The agency also declines to replace the 15-day reporting period with an annual reporting requirement as suggested by the second comment. The withdrawal of an approved NDA drug product may affect the marketing of duplicate ANDA drug products, so timely reports of drug product withdrawals may be very important.

Section 314.92—Drug Products for Which Abbreviated Applications May be Submitted

FDA received four comments on proposed § 314.92. The proposed rule

stated that abbreviated applications are suitable for certain drug products, such as drug products that are the same as a listed drug, drug products that meet the monograph for an antibiotic drug for which FDA has approved an application, drug products for which FDA has found an ANDA to be suitable and has announced such a finding in the *Federal Register*, and drug products that FDA has declared to be suitable for an ANDA submission under the petition procedures.

16. One comment asked FDA to refuse ANDA's for DESI drugs on the grounds that the statute only applies to post-1984 ANDA's. The comment noted that DESI drugs are reviewed by category rather than active ingredient and said some DESI active ingredient categories lack a "readily identifiable pioneer NDA product." Another comment supported ANDA's for DESI drugs.

The ANDA provisions of the 1984 amendments are applicable to all generic drugs for which approval is sought after September 24, 1984, the date on which the statute was enacted. Perpetuating different ANDA systems for pre-1982 drugs and post-1982 drugs would be needlessly confusing, illogical, and inefficient to FDA, the public, and industry. Therefore, FDA has included DESI drugs in these regulations.

Upon further consideration, FDA agrees that ANDA's may be inappropriate for some DESI drug products. In the DESI process, a DESI-reviewed NDA or ANDA is usually considered approved for safety and effectiveness through the approval of a supplement that brings the NDA or ANDA drug product into compliance with a DESI-upgrade notice. The DESI-upgrade notice describes what information the NDA or ANDA holder must provide in order for its drug product to be considered effective. If the NDA or ANDA holder complies with the notice through an approved supplement, then the drug product is considered to be safe and effective and can be listed in the Orange Book. Once this occurs, a person may be able to submit an ANDA for the product. However, if the NDA or ANDA holder fails to comply with the notice, the NDA or ANDA drug product is not considered to be approved for effectiveness and cannot be a listed drug. Under these circumstances, an ANDA cannot be submitted because there is no "listed drug." Therefore, FDA has revised § 314.92 by removing paragraph (a)(3) and renumbering paragraph (a)(4) as (a)(3). An applicant seeking to rely on the findings reflected in a DESI-upgrade notice, in the absence of a listed drug, should submit its

application under section 505(b)(2) of the act.

Once a drug subject to a DESI notice is approved for safety and effectiveness and can serve as a listed drug, the agency will require the submission of an ANDA under section 505(j) of the act for a generic version of the product. As a matter of policy, the agency does not accept applications under section 505(b)(2) of the act when there is a listed drug that would provide a basis for an application under section 505(j) of the act. For clarity, FDA has added a new paragraph (d)(9) in § 314.101. The issue had been discussed in the preamble to the proposed rule (54 FR 28890 through 28891). At that time, the agency proposed to treat a 505(b)(2) application as submitted under section 505(j) of the act if the application was for a duplicate of a listed drug eligible for approval under section 505(j) of the act. Id. FDA believes that the policy it is describing in new § 314.101(d)(9), that an application for a drug such as this needs to be submitted by the applicant as an ANDA under section 505(j) of the act, is the preferable approach.

17. Two comments concerned proposed § 314.92(a)(1), which said, in part, that an ANDA would be suitable for a drug product that is the same as a listed drug and that the term "same as" means "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." The proposed rule would also require potential applicants to comply with § 314.122, "Submitting an abbreviated application for or a 505(j)(2)(C) petition that relies on, a listed drug that is no longer marketed," if the listed drug had been voluntarily withdrawn or not offered for sale by its manufacturer. One comment asked FDA to define "strength." The second objected to the language on voluntary withdrawals. The comment said NDA holders should disclose the reasons for withdrawing a product, and FDA should determine whether those reasons raise safety or efficacy questions, and then give ANDA holders an opportunity to examine and respond to the information on the withdrawal.

"Strength" refers to the amount of the product's active ingredient and is usually expressed in terms of weight. For example, a drug that is available as a 50 milligram (mg) tablet and a 100 mg tablet has two "strengths."

As for voluntary withdrawals and the reasons for a withdrawal, FDA refers

the reader to its discussion of identical comments at § 314.161 below.

17a. Additionally, although the preamble to the proposed regulation stated: "Section 507(a) of the act permits the submission of abbreviated applications for *duplicates* of all antibiotics the agency has already approved for marketing" (emphasis added) (54 FR 28872 at 28878) the proposed regulation (§ 314.92(a)(2)) referred only to products that meet the monograph. Because, in some instances, a generic antibiotic may be a duplicate of an approved antibiotic but may not meet the monograph in every respect for that approved antibiotic, the agency has broadened the language of the proposed regulation to include generic antibiotics that either are duplicates of, or meet the monograph for, the approved antibiotic. This change is made at the agency's initiative to reflect the intent of the agency expressed in the preamble to the proposed regulation.

Section 314.93—Petition To Request a Change from a Listed Drug

Proposed § 314.93(b) stated that a person who wants to submit an ANDA for a drug product "which is not identical to a listed drug product in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an abbreviated application."

18. Most comments agreed with the proposal, but one comment suggested that the rule be revised to state that FDA will not accept a suitability petition if the proposed drug product has different inactive ingredients which "may have some effect on the safety or efficacy of the altered product." Another comment asserted that the safety and effectiveness of a proposed new combination drug cannot be determined without drug interaction data.

FDA declines to accept the comments. Under the statute, suitability petitions are for drugs that have a different active ingredient, route of administration, dosage form, or strength. (See 21 U.S.C. 355(j)(2)(C).) A person seeking marketing approval of a drug product that differs from the listed drug product only with respect to inactive ingredients is not required to submit a suitability petition. FDA also notes that § 314.94(a)(9)(ii) requires applicants to identify and characterize the inactive ingredients used in the proposed drug product, and this information should permit FDA to determine whether the different inactive ingredients affect the product's safety. If FDA determines that the inactive

ingredients of the drug are unsafe, the agency will refuse to approve the ANDA. (See 21 U.S.C. 355(j)(3)(H); 21 CFR 314.127.)

As for proposed new combination drug products, the statute expressly authorizes petitions for drugs with one different active ingredient. The petitioner must provide information to show that the different active ingredient is "an active ingredient of a listed drug or a drug which does not meet the requirements of section 201(p)" (21 U.S.C. 355(j)(3)(C)(iii)(II)). Although the statute does not expressly require drug interaction data, it authorizes FDA to refuse to approve a petition if "investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients" or if a drug product containing a different active ingredient "may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application" (21 U.S.C. 355(j)(2)(C)(i) and (j)(2)(C)(ii)). Thus, if the agency determines that the safety and effectiveness of a proposed combination drug product cannot be shown without drug interaction data, FDA will not approve the petition. FDA has, on its own initiative, revised the language in § 314.93(d) to clarify the circumstances under which a petitioner may identify more than one listed drug. The revised language corresponds more closely to the statutory language.

19. One comment suggested that the agency revise proposed § 314.93(d)(3) regarding proposed combination drug products with one different active ingredient. The proposed rule would require petitioners to provide information to show that:

If the proposed drug product is a combination product with one different active ingredient, including a different ester or salt, from the reference listed drug, that the different active ingredient has previously been approved in a listed drug or is a drug that does not meet the definition of "new drug" in section 201(p) of the act.

The comment suggested that § 314.93(d)(3) be revised to state that ingredients listed as Category I (generally recognized as safe or generally recognized as effective) in a tentative final or final OTC monograph are "substitutable ingredients."

FDA declines to revise the rule as requested. The rule is consistent with section 505(j)(2)(A)(ii)(III) of the act, which states that the different active ingredient must be "an active ingredient of a listed drug or of a drug which does not meet the requirements of section 201(p)." Therefore, in order to be a "substitutable ingredient," a Category I

ingredient must be either an active ingredient of a listed drug or an active ingredient that does not meet the definition of a "new drug." An ingredient included in a final OTC drug monograph would be a "substitutable ingredient" because it does not meet the definition of a "new drug."

20. One comment asked FDA to accept petitions to submit an ANDA for a product whose labeling differs from the reference listed drug by being "more clear or offer better directions regarding how the drug should be taken."

FDA declines to accept the comment. Suitability petitions are for drugs that have a different active ingredient, route of administration, dosage form, or strength. (See 21 U.S.C. 355(j)(2)(C).) Labeling differences, therefore, are not proper subjects for a suitability petition.

FDA reminds applicants that the labeling for an ANDA product must be the same as the labeling for the listed drug product except for differences due to different manufacturers, exclusivity, etc. (See 21 U.S.C. 355(j)(3)(G).) An ANDA applicant who believes that the labeling for a proposed drug product should differ from that approved for the reference listed drug should contact FDA to discuss whether labeling for both generic and listed drugs should be revised.

21. One comment objected to proposed § 314.93(e)(1)(v) because FDA would refuse to approve a petition if the reference listed drug had been voluntarily withdrawn from sale and FDA had not determined whether the withdrawal was for safety or effectiveness reasons. The comment would revise the rule to require manufacturers to provide detailed reasons for withdrawing a drug product and, if FDA concluded that those reasons involved safety or effectiveness issues, require FDA to provide this information to prospective ANDA applicants or petitioners.

FDA declines to amend the rule as requested. The statute does not require FDA to determine why a listed drug was withdrawn from sale in every case, and the agency believes it would be impractical to do so. The agency discusses this subject in greater detail in its discussion of the comments to 21 CFR 314.151 through 314.152.

22. Five comments focused on the term "limited confirmatory testing" mentioned in the preamble to proposed § 314.93(e)(2). Proposed § 314.93(e)(2) stated that the phrase, "investigations must be conducted," meant "information derived from animal or clinical studies is necessary to show that the drug product is safe or effective." The

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preamble to the proposed rule explained that:

If preclinical or clinical data are needed to support safety, or if clinical data are needed to support the effectiveness of the requested change, then an abbreviated new drug application is not appropriate for the proposed drug product, and FDA will not approve a petition. However, under certain circumstances, data from limited confirmatory testing to show that the characteristics that make the proposed drug product different from the listed drug do not alter its safety and effectiveness may be accepted in a petition or an additional data to be included in an ANDA resulting from an approved petition.

54 FR 28872 at 28880.

One comment asked FDA to define "limited confirmatory testing." Two comments noted that the preamble to the proposed rule would permit limited confirmatory testing but that the rule itself would not approve a petition if animal or clinical studies are needed. The comments suggested revising the rule so a drug product "for which any testing other than bioavailability testing is required is ineligible for ANDA treatment." Two other comments said limited confirmatory testing would create a new class of applications or permit firms to avoid full NDA requirements; these comments would eliminate such testing or limit their use to "very rare circumstances."

As stated in the preamble to the proposed rule, by "limited confirmatory testing," FDA means "simple studies intended to rule out unlikely problems." (See 54 FR 28872 at 28880.) Such tests do not include animal or clinical studies whose information is necessary to show that the drug is safe or effective. (See 21 CFR 314.93(e)(2).) Thus, FDA does not intend to permit petitioners to substitute limited confirmatory testing for clinical studies or otherwise circumvent NDA requirements.

23. One comment objected to the language in proposed § 314.93(e)(3), which said FDA may "at any time during the course of its review of an abbreviated new drug application, request additional information required to evaluate the change approved under the petition." The comment argued that this language would permit FDA to revoke its approval of a petition even after an ANDA is submitted.

When read in its entirety, § 314.93(e)(3) states that when FDA approves a petition, the agency may describe what additional information, if any, will be required to support an ANDA for the drug product, and that this approval should not be construed as preventing FDA from requesting additional information to evaluate the

ANDA. Thus, the provision concerns information needed to support approval of the ANDA rather than the information needed to evaluate the petition.

As for "revoking" approval of a suitability petition, FDA is amending § 314.93 by adding a new paragraph (f) to give the agency express authority to withdraw approval of a suitability petition if new information indicates that approval should be withdrawn. Such information can come from any source, including ANDA's submitted under the petition. This amendment will ensure that suitability petition approvals continue to reflect valid, scientific judgment and reasoning and prevent would-be ANDA applicants from relying on suitability petitions that, in light of new information, would not have been granted had the new information been available when the petition was under consideration.

Section 314.94—Content and Format of an Abbreviated Application

FDA received over 100 comments pertaining to ANDA format and content. Most recommended revisions or clarification while several expressed general agreement with specific provisions.

Table of Contents

24. One comment suggested that proposed § 314.94(a)(2), which would require the archival copy of an ANDA to contain a table of contents, be revised to require that both archival and review copies of an ANDA contain a table of contents.

Although the provision in question only pertains to archival copies of an application, FDA agrees with the comment and has amended § 314.94(d)(2) accordingly.

Basis for an ANDA Submission

25. Two comments addressed reference listed drugs under proposed § 314.94(a)(3)(i). The proposed rule would require an ANDA to contain "the name of the reference listed drug, including its dosage form and strength." The comments noted that the preamble to the proposed rule stated that the pioneer drug would "usually" be the reference listed drug, but, if more than one listed drug existed for the same drug product, the preamble recommended that applicants contact the Director of the Division of Bioequivalence before selecting a reference listed drug (54 FR 28880-28881). The comments asked FDA to explain how FDA determines which drugs should be reference listed drugs, and one comment proposed that the pioneer drug serve as the reference

listed drug "unless there are sound scientific reasons for which a substitution may be preferred."

As stated above, FDA has revised the rule so that FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA. Once FDA designates that reference listed drug, that drug will continue to be the reference standard even if the drug is later replaced as the market leader. The Orange Book will identify all reference listed drugs, so applicants are no longer instructed to call the Director of the Division of Bioequivalence. FDA has, however, deleted the language regarding Federal Register notices from § 314.94(a)(3)(i). As discussed elsewhere in this rule, the agency no longer regards a DESI notice as a listed drug and will not accept an ANDA in the absence of a listed drug.

Active Ingredients

26. Two comments sought more exacting standards or requirements for establishing that a generic drug and a listed drug contain the "same" active ingredients. Proposed § 314.94(a)(5)(i) would require an ANDA to contain information to show that the active ingredient in a single-active-ingredient product to be "the same as that of the reference single-active-ingredient listed drug." One comment stated that the active ingredients in the proposed drug product must be identical to those in the reference listed drug and that blood level comparisons are inadequate to establish such identity. The comment added that the rule should provide technical or scientific criteria for determining whether two active ingredients are equivalent.

The second comment would require applicants to demonstrate that their active ingredients "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics

and solid state forms of the drug have not been altered."

Under the statute, an ANDA applicant must show that its active ingredient is the same as that in the reference listed drug (21 U.S.C. 355(j)(2)(A)(ii)). FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (U.S.P.). However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness. For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required. Should questions arise, an applicant should contact the Office of Generic Drugs to determine what information would be necessary to demonstrate that its active ingredient is the same as that in the reference listed drug.

As for possible impurities or residues in the ANDA product, ANDA applicants would be required to provide information on the drug substance and the drug product as part of the chemistry, manufacturing, and controls section of the application. (See 21 CFR 314.94(a)(9); 314.50(d)(1).) This would include information on Impurities and residues. The "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" suggests that impurities "should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort." This guideline adds that "All major impurities should be individually limited. The maximum amount per unit dose of every individual impurity should be provided. If there is information on toxicity or information on toxic limits that have been set of these impurities, this information should be provided." If the manufacturing, packing, or processing controls cannot ensure the product's identity, strength, quality, and purity, or if the drug's composition is unsafe, FDA will not approve the ANDA. (See 21 U.S.C. 355(j)(3)(A) and (j)(3)(H).)

27. One comment sought clarification of proposed § 314.94(a)(5)(ii)(A). That provision would require an ANDA for a combination drug product to contain information to show that the active ingredients are the same as those for the reference listed drug, or:

"If one of the active ingredients differs from one of the active ingredients of the reference listed drug and the abbreviated application is submitted pursuant to the approval of a petition under § 314.93 to vary such active ingredient, information to show

that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug. Information to show that the different active ingredient of another listed drug or of a drug which does not meet the definition of a "new drug" in section 207(p) of the act, and such other information about the difference active ingredients that FDA may require.

The comment asked FDA to clarify the phrase "such other information" about the different active ingredient that FDA may require."

The phrase quoted by the comment reflects the statutory language at section 505(j)(2)(A)(ii)(III) of the Act. FDA has not requested any additional information from applicants under this authority, and cannot predict what type of information it would require. Nevertheless, the final rule keeps this language and will not foreclose its use.

Bioequivalence

FDA received nine comments on proposed § 314.94(a)(7). That section describes the kinds of information required to demonstrate bioequivalence.

28. One comment suggested that applicants be given the option of submitting a proposed bioavailability or bioequivalence study protocol for review and comment either as part of an ANDA or before submitting an ANDA so that applicants do not conduct questionable or unnecessary studies.

Since publication of the proposed rule, FDA has changed its policies regarding the submission of incomplete ANDA's. Under earlier policy, FDA permitted ANDA applicants to submit ANDA's with bioequivalence study protocols and to provide bioequivalence study data at a later date. This policy has resulted in a significant and unwarranted expenditure of resources in reviewing applications that had little potential for approval. FDA will therefore no longer accept an ANDA that does not contain complete bioequivalence study data if such data are required for approval. However, with respect to pre-ANDA submissions of bioequivalence protocols, FDA will continue, to the extent that time constraints and resources permit, to provide guidance on such protocols before an ANDA is submitted. Applicants wishing such guidance may submit requests for review of proposed protocols to the Director, Division of Bioequivalence. The Division will attempt to provide informal comments on such submissions as time and resources permit. The agency has also revised § 314.94(a)(7)(i) to delete the language concerning Federal Register notices. As stated earlier, the agency no longer regards a DESF notice as a listed drug and will not

accept an ANDA in the absence of a listed drug.

29. One comment recommended that FDA give each holder of an NDA for an innovator drug an opportunity to comment on any bioequivalence study protocol proposed by an ANDA applicant if "nonabsorbed drugs" are involved. The comment would also establish deadlines for the NDA holder to respond to the protocol and for FDA to issue a decision.

FDA has considerable scientific expertise in the critical review of bioequivalence protocols. If additional expertise is necessary, the agency will seek advice from sources such as the Generic Drug Advisory Committee on an "as needed" basis. The agency also notes that, as a basic matter, giving NDA holders a role in reviewing the applications of potential competitors could create a conflict of interest and compromise an applicant's confidential information. Therefore, FDA is not adopting the comment.

30. One comment stated that an FDA request for additional information under proposed § 314.94(a)(7)(ii) should be made within 30 days after the initial submission of the ANDA. As drafted, proposed § 314.94(a)(7)(ii) would require an ANDA submitted under a suitability petition to vary an active ingredient to contain "the results of any bioavailability or bioequivalence testing required by the agency, and any other information required by the agency to show that the different active ingredient is of the same pharmacological or therapeutic class as that of the changed ingredient in the reference listed drug, and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug."

FDA declines to accept the comment. If FDA determines, after receiving an ANDA that was submitted pursuant to an approved suitability petition, that the ANDA applicant must submit additional information, this determination represents a finding that the information is necessary to ensure that the proposed ANDA drug product has the same therapeutic effect as the reference listed drug. (See 21 U.S.C. 355(j)(2)(A)(iv).) The agency will not, therefore, forego requesting such information simply because a specific time period has expired. FDA will act on ANDA's as expeditiously as agency resources and priorities permit, but cannot guarantee that the agency will be able to identify, within 30 days, all instances where it needs to request information.

31. One comment interpreted proposed § 314.94(a)(7)(ii) to mean that

safety and efficacy studies could be required and asked FDA to state that a product requiring more than bioequivalence testing cannot be the subject of an ANDA.

FDA will not require safety and effectiveness investigations under § 314.94(a)(7)(ii). As stated in section 505(j)(2)(C) of the act and § 314.93(e)(1)(i), if clinical investigations are needed to establish a product's safety or effectiveness, that product is not suitable for approval under an ANDA. FDA does not, however, interpret this section to preclude the use of data to demonstrate whether a proposed drug product will have the same therapeutic effect as a reference listed drug.

FDA has, however, revised § 314.94(a)(7)(ii) to state that an ANDA submitted under an approved petition must contain the results of any bioavailability or bioequivalence testing or any other information required by FDA to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. This change encompasses ANDA's for single-ingredient drug products submitted pursuant to an approved suitability petition. The proposed rule inadvertently omitted a reference to such ANDA's and unintentionally created a potential problem for some ANDA applicants. For example, if the approved suitability petition permitted a change in dosage form, it might be difficult for some applicants to demonstrate bioequivalence between the new dosage form and the dosage form of the reference listed drug, e.g., between a cream and a tablet. The change corrects this problem and corresponds to the statutory language in section 505(j)(2)(A)(iv) of the act.

32. Proposed § 314.94(a)(7)(ii)(A) stated that FDA would consider a proposed drug product to have the same therapeutic effect as a reference listed drug if the applicant provided information demonstrating that:

There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product of the same safety and effectiveness.

One comment would delete the adjective "same" from the phrase "of the same safety and effectiveness" because "[i]t may not be possible to have exactly the same safety and effectiveness.

effectiveness, for example, if a different active ingredient is included in a combination product and safety or efficacy is enhanced." The comment recommended replacing the words "of the same safety and effectiveness" with "whose safety and effectiveness have not been adversely affected."

FDA agrees and has revised the rule accordingly.

33. One comment suggested amending proposed § 314.94(a)(7)(iii) to state that waivers from the in vivo bioavailability or bioequivalence requirement are possible under 21 CFR 320.22. As drafted, proposed § 314.94(a)(7)(iii) made no reference to waivers.

FDA declines to adopt the suggestion. Section 314.94(a)(7), generally, and § 314.94(a)(7)(iii), specifically, do not require in vivo bioequivalence. The provisions state the statutory requirement that an ANDA contain information to show bioequivalence and that, if that information is obtained from an in vivo study, the applicant include in its application information about the analytical and statistical methods used and information to show that the study was conducted in compliance with 21 CFR parts 50 and 58. Information to show bioequivalence may, depending on the drug product, come from an in vivo or an in vitro study.

34. Two comments focused on institutional review board (IRB) and informed consent requirements at proposed § 314.94(a)(7)(iii). The proposed rule would have required a statement regarding compliance with the IRB and informed consent requirements at 21 CFR parts 58 and 50, respectively, for each in vivo bioequivalence study in an ANDA. One comment asked FDA to identify the party responsible for providing a statement on IRB review and informed consent. The comment suggested that the "sponsor," which FDA presumes is the ANDA applicant, make such statements only after the sponsor had conducted an "appropriate on-site inspection of the records and the informed consent process as the study is performed." The second comment suggested revising the regulation to identify the party making the statement. The comment explained that sponsors who have transferred their obligations to contract research organizations should be able to provide the names and addresses of such organizations rather than make the statements on IRB review and informed consent themselves.

FDA declines to accept the comments. The ANDA applicant is ultimately responsible for ensuring that the ANDA satisfies all statutory and regulatory obligations, including IRB review under 21 CFR part 58 and informed consent

under 21 CFR part 50. This is true even if the ANDA applicant has elected to use a contract research organization to conduct the study. If an ANDA does not contain such a statement, FDA may refuse to receive it. (See § 314.101(b)(3); see also § 314.101(d)(7).)

Labeling

Proposed § 314.94(a)(8) set forth labeling requirements for ANDA's. The proposal would require applicants to provide copies of the currently approved labeling for the reference listed drug, labels and labeling for the proposed drug product, and a statement that the applicant's proposed labeling is the same as that for the reference listed drug except for certain differences, including, but not limited to, differences due to exclusivity or patent protection. The proposal, at § 314.94(a)(8)(iv), would also require applicants to provide a side-by-side comparison of the applicant's proposed labeling with the approved labeling for the reference listed drug. The proposed rule did not state how applicants could acquire copies of the reference listed drug's labeling, but the preamble said current approved labeling could be obtained under the Freedom of Information Act (FOIA) (54 FR 28872 at 28884).

35. Several comments stated that obtaining copies of drug labeling under FOIA would be time-consuming, difficult, or impractical. The comments suggested that FDA develop procedures to display such labeling or to provide them to applicants upon written or oral request. One comment also said that FDA should routinely provide ANDA applicants with updated labeling.

FDA disagrees that its FOIA system is inadequate for ANDA labeling purposes. The agency's FOIA system handles information requests in an orderly and expeditious manner. The procedure for requesting information is both simple and straightforward. (See 21 CFR 20.40.) Additionally, FDA regulations, in most instances, require the Freedom of Information Staff to respond to a freedom of information request within 10 working days. (See 21 CFR 20.41(b).) For these reasons, FDA declines to create an alternate system for providing drug labeling.

As for providing updated labeling information, the agency does not believe it is currently feasible to routinely provide updated labeling on all products eligible for ANDA's. The Office of Generic Drugs (OGD) encourages applicants to contact OGD before submitting an ANDA for advice on what labeling would be the most appropriate to use for its proposed product. Such

labeling can ordinarily be obtained from one or more of the following sources, including (1) OGD labeling guidance documents, (2) the innovator or generic drug product labeling from the product itself, (3) Physician's Desk Reference, (4) FDA's Freedom of Information Office, or (5) calling the Drug Information Services Branch directly at 301-443-3910. FDA also provides further guidance to an ANDA applicant after the applicant submits proposed labeling. After ANDA approval, FDA tracks the labeling status of the pioneer drug product and, if necessary, notifies ANDA holders when and how they must revise their labeling.

36. One comment asked FDA to clarify its policy regarding the use of the ANDA holder's name on the label and package insert when the ANDA holder neither manufactures nor distributes the drug product.

FDA's policy regarding the names on drug product labeling is set forth at 21 CFR 201.1 as authorized by section 502 of the act (21 U.S.C. 352). In general, § 201.1 states that, with few exceptions, no person other than the manufacturer, packer, or distributor may be identified on the label of a drug or drug product. The Orange Book discusses this subject in greater detail and recognizes that, under certain circumstances, the ANDA holder's name might not appear on the product's labeling. (See "Approved Drug Products with Therapeutic Equivalence Evaluations," pp. 1-3 (1991).)

37. One comment asked how ANDA applicants should present proposed labeling. The comment said that FDA should specify its exact requirements or permit applicants to submit labeling in any format they choose.

FDA believes that detailed instructions on the size and format of proposed labeling are not appropriate for this regulation. Applicants who have questions about the presentation of labeling in ANDA's should contact the Program Support Staff, Office of Generic Drugs, for guidance.

38. Proposed § 314.94(a)(8)(ii) would require ANDA applicants to provide copies of the label and labeling for the proposed drug product. Two comments suggested that FDA amend the rule to permit applicants to provide photographs of labeling rather than actual copies of the labeling when the label is printed on a tube or shipping carton.

FDA declines to accept the comment. Actual copies of tube labeling and other labeling help FDA determine the prominence of the information presented and whether the information is legible. These determinations cannot be easily made by the review of photographs. Ordinarily, however, FDA does not

require submission of copies of shipping carton labeling as part of an abbreviated application.

39. Two comments opposed the requirement for a side-by-side comparison between the proposed ANDA drug product's labeling and the reference listed drug product's labeling under proposed § 314.94(a)(8)(iv). The comments said the comparison would be cumbersome and impractical, and suggested annotated changes or highlighted changes instead of comparisons.

In contrast, three comments supported side-by-side labeling but asked that ANDA holders be required to complete labeling revisions within 30 days of any change in the listed drug's labeling or to provide labeling comparisons every 8 months to ensure that the ANDA drug's labeling matched that of the listed drug. One comment said FDA should create a mechanism to compel ANDA holders to revise their labeling to conform to the listed drug product once the ANDA is approved.

The final rule retains the requirement of side-by-side labeling comparisons. Side-by-side comparisons enable FDA reviewers to readily identify differences between the ANDA applicant's and the innovator's product labeling. FDA does not believe that this requirement will impose a significant burden on ANDA applicants.

As for creating a mechanism to compel labeling revisions, section 505(e)(2) of the act authorizes the withdrawal of approval of an application if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." This provision applies to both ANDA and NDA drug products. Because an ANDA must have labeling that is the same as the reference listed drug under section 505(j)(2)(A)(v) of the act, FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling. FDA, therefore, has revised § 314.150 to permit the agency to withdraw approval of an ANDA if the applicant fails to maintain labeling in compliance with the requirements of the act.

As for requiring ANDA holders to submit drug labeling at periodic intervals, FDA believes that the existing reporting requirements at 21 CFR 314.70

and 314.81 ensure that labeling changes are brought to FDA's attention in an appropriate and timely fashion. The agency will advise ANDA holders of changes to be made after approval, but postapproval changes resulting from the expiration of exclusivity or patent protection are the responsibility of the ANDA holder.

40. Two comments said the labeling provisions should be revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information. One comment added that ANDA applicants should be allowed to delete some of the indications contained in the labeling for the reference listed drug.

FDA disagrees with the comments. Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. (See 54 FR 28872 at 28884.) If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

41. One comment suggested revising proposed § 314.94(a)(8)(iv) to exempt ANDA holders from being required to submit pharmacokinetic data to support new labeling unless the new labeling pertained to serious health or safety effects. The proposed provision stated that differences between an ANDA applicant's proposed labeling and the labeling approved for the reference listed drug may include, among other things, differences in pharmacokinetics. The comment explained that "insignificant labeling changes otherwise could become a tool to impede the ability of generics to compete, or force them to raise prices to the consumer in order to absorb the cost of additional, insignificant and, perhaps, unnecessary pharmacokinetic studies."

The comment misinterpreted the proposed requirement. The provision

does not impose a pharmacokinetic data requirement for all labeling changes. In fact, FDA believes that most labeling changes that do not involve serious health or safety effects will be acceptable without new pharmacokinetic data. However, FDA also believes that some labeling changes may be formulation-specific and that such changes may require additional pharmacokinetic data (e.g., addition of a bioequivalence statement). FDA, therefore, reserves the right to examine such labeling changes on a case-by-case basis to determine whether additional pharmacokinetic data are necessary before the ANDA holder changes labeling.

42. One comment proposed revising the third sentence in proposed § 314.194(a)(8)(iv), which listed certain permissible labeling differences between the ANDA drug product and the reference listed drug, to read as follows:

Such differences protected by patent or accorded exclusivity by 505(j)(4)(D) of the act between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

The comment explained that the revision would protect ANDA applicants from "a possible claim of inducement or infringement where a nonapproved, but patented, method of administration is discussed in the innovator's label" or the labeling refers to more than one method of use and "some but fewer than all of the methods of use are entitled to nonpatent exclusivity."

FDA agrees in part with the comment and has amended the provision to state that differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include omissions of an indication "or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act."

Chemistry, Manufacturing, and Controls

FDA received a number of comments on the chemistry, manufacturing, and controls section of an ANDA.

43. Many comments sought further definitions or explanations regarding ANDA chemistry, manufacturing, and controls documentation requirements, including information on technical details, such as determining the source of impurities, potential degradation, and

test methodologies. Two comments asked FDA to develop guidelines on acceptable levels of preservatives and other inactive ingredients.

These comments raise technical questions that are beyond the scope of this rule. FDA has already issued a number of guidelines addressing many of the questions. These guidelines apply to both full and abbreviated applications, and a list of available guidelines may be obtained from CDER Executive Secretariat Staff, Center for Drug Evaluation and Research (HFD-8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. FDA will consider the comments in determining whether to revise existing guidelines or to develop new guidelines.

44. Several comments objected to the provisions in proposed § 314.94(a)(9) requiring ANDA applicants to use the same inactive ingredients as the reference listed drug or to identify and characterize the differences between inactive ingredients. The comments stated that ANDA applicants might not know or might be unable to discover all inactive ingredients used in the reference listed drug. The comments suggested that FDA either not require that the inactive ingredients be the same or require the disclosure of the inactive ingredients used in the reference listed drug.

Because the labeling regulations do not require listing of inactive ingredients for drug products in an oral dosage form (see 21 CFR 201.100(b)(5)), ANDA applicants may be unable to discover what inactive ingredients were used in such drug products. Consequently, FDA has revised § 314.94(a)(9) to require ANDA applicants to include such a comparison only for drug products intended for parenteral use, ophthalmic or otic use, or topical use. ANDA applicants will be able to determine the inactive ingredients in reference listed drugs for these dosage forms because such ingredients are disclosed on the labeling. (See 21 CFR 201.100(b)(5).) For other drug products, FDA has revised § 314.94(a)(9)(ii) to require applicants only to identify and characterize the inactive ingredients in the proposed drug product and to provide information demonstrating that the inactive ingredients do not affect product safety.

45. Proposed § 314.94(a)(9)(iv) stated, in part, that:

* * * an applicant may seek approval of a drug product intended for ophthalmic or otic use that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not

affect the safety of the proposed drug product, except that in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(54 FR 28872 at 28923).

One comment objected to the example involving balanced salt solutions and isotonic saline solutions in proposed § 314.94(a)(9)(iv). The comment explained that changes in an ophthalmic buffer or tonicity agent from isotonic saline to balanced salt solutions do not raise serious safety questions, and FDA cannot presume that such changes are to claim a therapeutic advantage.

When read in its entirety, the second sentence in § 314.94(a)(9)(iv) simply states that an applicant whose product is intended for ophthalmic use cannot change a buffer or substance to adjust tonicity "for the purpose of claiming a therapeutic advantage over or difference from the listed drug" * * *. The rule does not state that use of a balanced salt solution as opposed to an isotonic saline solution would be impermissible in itself or that FDA would presume such changes to be for claiming a therapeutic advantage. Determining whether the applicant claims a therapeutic advantage over or difference from the listed drug depends on the circumstances surrounding each case.

Samples

46. FDA received one comment regarding generic drug product samples under proposed § 314.94(e)(10). The proposed rule would require ANDA applicants to comply with the sampling provisions at 21 CFR 314.50 (e)(1) and (e)(2) but would not require ANDA applicants to submit samples until FDA requested them. The comment suggested revising the rule to require ANDA applicants to obtain samples and to retain them in their stability containers for all lots of a finished product. The comment added that FDA should "make itself available as a witness if requested for the distribution of samples to laboratories for bioavailability studies."

Under existing current good manufacturing practice (CGMP) regulations, manufacturers are already required to retain samples. (See 21 CFR 211.84 and 211.170.) FDA has also issued an interim rule that requires applicants who conduct in-house bioavailability and bioequivalence testing and contract laboratories who conduct such testing to

retain reserve samples of the drug products used to conduct the studies. The interim rule, which appeared in the *Federal Register* of November 8, 1990 (55 FR 47034), and existing CCMR regulations will help FDA ensure that the samples sent to laboratories match the drug product to be produced. Therefore, the suggestion that FDA be available to witness distribution of samples to laboratories is unnecessary. FDA anticipates publication of a final rule shortly.

Potent Certification

FDA received a number of comments regarding patent certifications under proposed § 314.94(a)(12). The agency is still examining these comments and will finalize the provisions for patent certification at a later date.

DESI Drugs

47. Two comments objected to the inclusion in proposed § 314.94(b) of DESI drugs in the ANDA regulations. The proposed rule would permit persons to file ANDA's for a duplicate of a drug product that is subject to the DESI review or a DESI-like review and also a listed drug. If the ANDA is for a drug product that is a duplicate of a drug product that is subject to the DESI review or a DESI-like review and not listed, the proposed rule would require applicants to comply with the conditions set forth in the applicable DESI notice or other notice with respect to conditions of use and labeling and the ANDA content and format requirements. One comment argued that the statute applies only to post-1984 ANDA's so including DESI drugs was inappropriate. The comment suggested deleting this provision but noted that "additional special considerations need to be recognized" when finalizing the rule because, for some DESI active ingredient categories, there is no readily identifiable pioneer NDA product. A second comment stated that, under proposed § 314.94(b)(2), DESI drugs cannot be reference listed drugs unless they are listed or the applicant has filed an application under section 505(b)(1) or (b)(2) of the act.

The ANDA provisions of the 1984 amendments are applicable to all generic drugs for which approval is sought after September 24, 1984, the date on which the statute was enacted. However, after careful consideration, FDA agrees that ANDA's are inappropriate if the drug product that is the subject of a DESI review or DESI-like review has not complied with the conditions for effectiveness set forth in a DESI notice or other notice. In the absence of an approved product that

satisfies the conditions set forth in the DESI notice or other notice, there is no "listed drug" within the provisions of section 505(j)(6) of the act, and an ANDA cannot be submitted for that drug.

Therefore, FDA will no longer accept an ANDA for a DESI drug product when there is no listed drug for that product, and has deleted § 314.94(b)(2) entirely. An applicant seeking approval of a drug product covered by a DESI upgrade notice before a product is approved for safety and effectiveness under that notice should submit a 505(b)(2) application to the Office of Generic Drugs. Generally the 505(b)(2) application must contain the information specified in section 505(b)(2) of the act, except that the labeling must meet the conditions of use announced as effective in the relevant DESI upgrade notice. In satisfying the full reports of investigations requirement under section 505(b)(1)(A) of the act, the applicant may refer to the agency's conclusions in the DESI upgrade notice about the product's safety and effectiveness and must demonstrate that the proposed drug product is bioequivalent to the drug product that is the subject of the relevant DESI upgrade notice. The agency will generally employ the same mechanisms and standards in approving a section 505(b)(2) application for a DESI drug product that it would for an ANDA under section 505(j).

Section 314.96—Amending on Unapproved ANDA

FDA received a small number of comments concerning proposed § 314.98. The proposed rule would permit applicants to amend an ANDA that had been submitted, but not yet approved, to revise existing information or to provide additional information. The proposed rule also explained when an amendment might extend the review period.

48. One comment objected to a preamble statement which said "data from a bioequivalence study where only a protocol was contained in the original submission" could be an example of a major ANDA amendment. (See 54 FR 28872 at 28888.) The comment said that an ANDA application should be complete when submitted and not completed through amendments.

FDA agrees with the comment. Under current policy, FDA does not accept an ANDA that contains only a bioequivalence study protocol. This policy is consistent with the statutory provision requiring an ANDA to contain information showing that the applicant's drug product is, rather than "will be shown to be," bioequivalent to the

reference listed drug. (See 21 U.S.C. 355(j)(2)(A)(iv).)

49. One comment asked whether ANDA applicants could amend applications without informing FDA of their intent to amend them or withdraw applications after receiving an approvable or not approvable letter.

Under 21 CFR 314.110(b), an ANDA applicant who has received an approvable letter must correct the deficiencies described in the approvable letter "by amendment within the specified time period" or FDA will refuse to approve the abbreviated application. The ANDA applicant may also ask the agency to provide an opportunity for a hearing. Under 21 CFR 314.120(b), an ANDA applicant who has received a not approvable letter must amend or withdraw the ANDA or notify FDA of an intent to file an amendment within 180 days after the date of the not approvable letter. Under 21 CFR 314.120(a)(3), an ANDA applicant may also ask the agency to provide an opportunity for a hearing. If an ANDA applicant fails to respond within 180 days to the not approvable letter, FDA will consider the ANDA applicant's failure to respond to be a request to withdraw the ANDA. Thus, an ANDA applicant that receives an approvable or not approvable letter may amend its ANDA without informing FDA of its intent to amend the ANDA. The regulations also do not require ANDA applicants to provide notice of intent to withdraw an ANDA.

50. Several comments discussed "major" and "minor" amendments in relation to proposed § 314.96(a)(2) and (a)(3). Proposed § 314.96(a)(2) would permit FDA to extend the review period if the amendment contained significant new data requiring additional time for agency review. Proposed § 314.96(a)(3) would treat the submission of an ANDA amendment to resolve substantial deficiencies as set forth in a not approvable letter as an agreement between FDA and the applicant to extend the review period 120 days. Neither provision referred to "major" or "minor" amendments, but the preamble to the proposed rule explained that a major amendment would be one which required substantial review time. The preamble provided several examples of such major amendments, including amendments containing data from a new bioequivalence study or stability or sterility study submitted in support of a drug product reformulation or changes in the manufacturing or controls procedures.

One comment stated that an amendment, regardless of whether it

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was a "major" or "minor" amendment, should not result in any extension of the review period if FDA had not begun to review the application. This comment also suggested that "minor" amendments, which it defined as requiring less than 8 hours of review time, only result in a 14-day extension to the review period.

FDA disagrees with the comment. A policy that would permit applicants to submit amendments containing significant data or information without extending the review period would encourage the submission of incomplete ANDA's and create new administrative problems between applicants and the agency. For example, disputes would arise as to whether an amendment had been submitted before review had begun or whether a particular FDA action constituted "review."

As for extension periods, FDA has decided not to adopt proposed § 314.96(a)(2). The agency found the proposed provision to be unfeasible and has decided to retain the concepts at § 314.60. Consequently, FDA has revised § 314.96(a)(2) to state that an amendment containing significant data or information requiring additional time for agency review will constitute an agreement by the applicant to extend the date by which the agency is required to reach a decision on the application. The revised paragraph states that FDA will ordinarily extend the review period "only for the time necessary to review the significant data or information," and this period will not exceed 180 days. This paragraph, as revised, is similar to the preexisting requirements under § 314.60 and encourages ANDA applicants to submit complete applications.

Proposed § 314.96(a)(2) also stated that FDA would notify an applicant of the length of the extension. The agency has decided not to adopt the notification provision. FDA's experience suggests that it is difficult and impractical to predict the length of an extension for an ANDA given the unpredictable nature of its workload. At the same time, FDA emphasizes that extensions under this paragraph will be "only for the time necessary to review the new information." The agency hopes to be able to limit extensions under § 314.96(a)(2), which applies to amendments submitted other than in response to a not approvable letter, to generally not more than 120 days if resources permit.

With regard to the comment regarding "minor" amendments, under current Office of Generic Drugs policy, FDA distinguishes between major and minor amendments only with regard to

amendments submitted in response to a not approvable letter. These are covered under § 314.96(a)(3).

51. Three comments concerned extending the review period for amendments under proposed § 314.96(a)(3). One comment suggested that the extension be "not more than 120 days." Another comment said major amendments responding to FDA reviewers should not constitute an agreement to extend the review period. This comment added that if an extension were necessary, "it should not affect the entire ANDA, but only the discipline in which it is generated." The third comment objected to § 314.96(a)(3) entirely and claimed, without explanation, that it was inconsistent with the statute.

As stated above with regard to § 314.96(a)(2), FDA has decided against the adoption of proposed § 314.96(a)(3) and, instead, has revised § 314.96(a)(3) to state that the submission of an amendment containing significant data or information to resolve deficiencies in the application as set forth in a not approvable letter constitutes an agreement between FDA and the applicant to extend the review period. This paragraph, as revised, corresponds to similar requirements under § 314.60. The extension will only be for the time necessary to review the significant data or information and would not exceed 180 days.

FDA notes that under current Office of Generic Drugs policy, FDA distinguishes between major and minor amendments submitted in response to not approvable letters. (See memorandum issued July 11, 1991, from the Director, Office of Generic Drugs, to Office Division Directors, Deputy Division Directors, Associate Office Directors, and Branch Chiefs.) FDA currently considers a minor amendment to be one that an experienced chemist reasonably can be expected to take less than 1 hour to complete the review. Under current policy, FDA commits to make every attempt to take action on a minor amendment within 60 days of its receipt, subject to applicable agency clearances such as a field inspection or microbiology consult.

Although the agency would like to be able to review all major amendments and applications within the 180-day period provided by statute, and would like to establish goals for reviewing these submissions in even shorter time periods, current resources do not provide a basis for establishing such goals for the foreseeable future. The Agency's goal at this time is to meet its obligations under the statute and to review these submissions as efficiently

and as expeditiously as possible without affecting the scientific integrity of the review.

The agency disagrees, however, with the comments that would prevent the agency from extending the review period. FDA's experience indicates that some amendments that are intended to respond to not approvable letters can be extremely complex and present new information. If the agency could not extend the review period after receiving such amendments, the only practical recourse would be not to approve the application and have the applicant submit a new ANDA. This would be inefficient and wasteful, so § 314.96(a)(3) treats an amendment under this paragraph as an agreement to extend the review period. This permits both FDA and the applicant to continue working on the ANDA.

FDA emphasizes, however, that an applicant who receives a not approvable letter and wishes to submit an amendment to resolve the deficiencies identified in the not approvable letter should confine its amendment to the subjects discussed in the letter. Completely new information on topics not raised in the not approvable letter only prolongs FDA review.

FDA disagrees with the comment claiming that the provision is inconsistent with the statute. Under section 505(j)(4)(A) of the act, FDA must approve or disapprove an application within 180 days after its initial receipt or "within such additional period as may be agreed upon . . ." The statute clearly recognizes that deciding whether to approve an application may require more than 180 days.

52. One comment said FDA should, upon submission of an ANDA, notify the applicant of the date on which the agency would approve or not approve the ANDA. Alternatively, the comment would require FDA to review an ANDA once it had been submitted to determine whether the application may be received.

FDA declines to adopt the comment. Under § 314.101(b)(2), FDA will notify applicants, in writing, whether the agency will receive an ANDA. (Such written notice, however, is not provided when FDA receives an ANDA supplement.) FDA will not, however, create a deadline for informing applicants whether an ANDA is received because such deadlines would be impractical. FDA cannot predict the number of applications it will receive in any given period and must remain flexible to assign its staff to respond to agency demands and priorities. As for notifying applicants of the latest date on

which FDA should approve or not approve an ANDA, § 314.100(a) states that FDA will send an ANDA applicant an approval letter, approvable letter, or not approvable letter within 180 days of receipt of an ANDA.

Section 314.97—Supplements and Other Changes to an Approved Abbreviated Application

FDA received no comments on this provision and has finalized it without change.

Section 314.98—Postmarketing Reports

Proposed § 314.98 would require an applicant that has an approved abbreviated antibiotic application or approved ANDA to comply with adverse drug experience reporting requirements. Proposed § 314.98(c), however, would not require holders of approved ANDA's or abbreviated antibiotic applications to submit periodic reporting of adverse drug experiences "if no adverse drug experience reports have been received and no labeling changes have been initiated by the applicant during the reporting interval."

53. Several comments, however, said postmarketing report requirements should be the same for NDA and ANDA holders. One comment said FDA should require ANDA holders to submit a periodic report that would indicate whether a company had received any adverse drug experience reports during the reporting period.

After careful consideration, FDA has revised § 314.98 to require ANDA applicants to submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports or initiated any labeling changes. As revised, the requirement is identical to that imposed on NDA holders. Periodic reports by ANDA holders will help FDA determine whether ANDA products have appropriate labelling and ensure that no adverse drug experiences go unreported.

54. FDA, on its own initiative, has amended § 314.98(a) to require abbreviated antibiotic application and ANDA applicants to comply with the recordkeeping requirements under § 314.80. This change corrects an inadvertent omission from the original proposal.

Section 314.99—Other Responsibilities of an Applicant of an Abbreviated Application

FDA received no comments on this provision and has finalized it without change.

Section 314.100—Timelines for Reviewing Applications and Abbreviated Applications; Section 314.101—Filing on Application and on Abbreviated Antibiotic Application and Receiving on Abbreviated New Drug Application

Proposed § 314.100 discussed timelines for reviewing applications and abbreviated applications. In general, the proposed rule would have FDA review an application or abbreviated application and send the applicant an approval letter, approvable letter, or not approvable letter within 180 days of receipt of an application under section 505(b) of the act, or an ANDA under section 505(j) of the act, or an abbreviated antibiotic application under section 507 of the act. Proposed § 314.101 concerned the circumstances under which FDA would file an application and an abbreviated antibiotic application and receive an ANDA. FDA received several comments suggesting additional agency obligations when an application or abbreviated antibiotic application is filed and when an ANDA is received.

55. One comment wanted the agency to amend proposed § 314.100 to require FDA to acknowledge receipt of an application and to issue an application number. The comment suggested that this occur within 14 days after the application is submitted.

Section 314.101 states that FDA will notify applicants, in writing, whether an application or abbreviated application is filed or received. (See 21 CFR 314.101(a)(2) and (b)(2).) These letters should contain an application number. As noted in paragraph 52 above, FDA believes that establishing a fixed time period for determining whether an application may be received would be impractical considering the number of applications and supplements FDA receives. As a result, FDA declines to amend the rule as requested.

56. Two comments suggested that either proposed § 314.100 or § 314.101 be amended to have FDA expressly determine whether an ANDA is "received" within 30 days of its submission.

FDA declines to accept the comments. As stated earlier, FDA cannot predict how many applications will be submitted in a given period, so it must retain flexibility to respond to any demands imposed on the agency. Creating an additional 30-day deadline in the ANDA review process would limit that flexibility without any significant benefit to FDA or to applicants.

57. Another comment said proposed § 314.101(b) should not authorize FDA to

determine whether an abbreviated application may be received.

FDA rejects this comment. By determining whether an application is "received," FDA encourages applicants to submit ANDA's that comply with statutory and regulatory requirements and are sufficiently complete for substantive review to begin. This conserves FDA resources by permitting FDA reviewers to devote their time to examining reviewable applications.

58. Two comments stated that an ANDA lacking bioequivalence or bioavailability information, completed bioequivalence studies, or stability data to support at least a 24-month expiration date should not be received.

As stated earlier, FDA no longer accepts an ANDA that lacks complete bioequivalence or bioavailability information at the time of its initial submission. Consequently, the agency has deleted § 314.101(d)(8), which pertained to ANDA's that did not contain the results of any required or completed bioequivalence or bioavailability study.

As for the comment suggesting that an ANDA lacking stability data to support at least a 24-month expiration date not be received, FDA declines to adopt the comment. Although most ANDA's contain such stability data, applicants have submitted and FDA has approved ANDA's containing stability data that support a different expiration date.

59. FDA received two comments on proposed § 314.101(e)(1). The proposed provision stated that FDA will refuse to file an application or abbreviated antibiotic application or consider an ANDA not to have been received if the drug product that is the subject of the submission "is already covered by an approved application or abbreviated application and the applicant of the submission is merely a distributor and/or repackager of the already approved drug product." One comment suggested that the first sentence be revised to state that FDA "may refuse to file" an application or abbreviated application if any of the listed conditions apply. The comment explained that FDA should have discretion to file an application, notwithstanding the existence of an approved application, when the applicant could justify the need for the duplicate application or abbreviated application. The second comment asked FDA to file duplicate ANDA's if two or more companies jointly develop the product or if an exclusive licensee or distributor seeks to file an ANDA with the licensor's consent.

Section 314.101(e)(1) was intended to prevent distributors from forcing FDA to

review applications for drug products that are already covered by approved applications. Reviewing an application is extremely time-consuming, and FDA's resources are limited. To permit applicants to force review of an application for a product that is already covered by an approved application would result in a severe drain on FDA resources to review duplicate applications, create duplicate product and patent listings in the Orange Book, and contribute to the agency's accumulation of applications. FDA did not, however, intend to apply this provision against companies that jointly develop a product. The agency, therefore, is amending § 314.101 to change the refusal in proposed § 314.101(e)(1) to accept duplicate applications to a discretionary refusal to accept duplicate applications under a new § 314.101(d)(8). FDA has also revised § 314.101(d)(8) to clarify that the agency may refuse to file an application or refuse to consider an ANDA to be received for a drug product when the application already has an approved application or abbreviated application for the same drug product.

Additionally, the agency has created a new § 314.101(d)(9) to clarify that the agency may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

60. One comment asked FDA to amend § 314.101(f)(2) to add time periods for setting a hearing date following ANDA disapproval and for issuing a decision on a hearing. The comment also requested procedures for appealing a disapproval that would give the applicant "immediate attention" and be considered to be "final agency action."

The regulation pertaining to not approvable letters to applicants, § 314.120, states that when the agency refuses to approve an application, abbreviated antibiotic application, or ANDA, it will give the applicant a written notice of an opportunity for a hearing under § 314.120(a)(3). Section 314.200 states that, if the Commissioner of Food and Drugs grants a hearing, the hearing will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval (§ 314.200(g)(5)). Thus, there is no need to amend § 314.101(f)(2) to set a hearing date.

FDA also declines to set a deadline for resolving hearings or appeals. The demands placed on the presiding officer and other FDA employees assigned to administrative hearings can be immense

depending on, among other things, the number of documents submitted to the administrative record. A large administrative record, coupled with the other obligations placed on the agency's employees, makes a deadline for resolving these matters impractical.

Finally, the administrative hearing regulations contain procedures for appealing a disapproval (e.g., 21 CFR 10.33 and 10.35). Parties may also seek judicial review as provided in 21 CFR 314.235(b).

Section 314.102—Communications Between FDA and Applicants

FDA received four comments regarding communications between FDA and applicants under proposal § 314.102. The proposed rule was substantially similar to the existing provision at 21 CFR 314.102 with the exception of new language to account for abbreviated applications and the availability of conferences and meetings for abbreviated applications. Proposed § 314.102(b) said FDA reviewers would make every reasonable effort to inform applicants of easily correctable deficiencies found in an application or abbreviated application or whether the agency would need more data or information. Proposed § 314.102(c) provided for 90-day conferences "to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies which have been identified by that time and which have not already been communicated." These conferences would be available for applications for all new chemical entities and major new indications of marketed drugs. Proposed § 314.102(d) would provide end-of-review conferences "to discuss what further steps need to be taken by the applicant before the application or abbreviated application can be approved." Finally, proposed § 314.102(e) indicated that applicants could request other meetings to discuss scientific, medical, or other issues.

61. One comment would require FDA reviewers to call ANDA applicants before issuing deficiency letters. The comment claimed FDA reviewers misinterpret or misread applications and could resolve these misunderstandings without a deficiency letter if they called ANDA applicants.

FDA declines to adopt the comment. The agency fully intends to communicate with ANDA applicants to resolve issues that arise during the ANDA review process but believes that requiring FDA reviewers to call ANDA applicants would be impractical and an inefficient use of resources. Some issues

cannot be resolved or adequately described in a telephone call.

62. One comment proposed amending § 314.102(d) to require FDA to hold an end-of-review conference within 30 days of the issuance of a not approvable letter. Two comments addressed meetings under proposed § 314.102(e). One comment would require FDA reviewers and chemists to meet with any applicant upon 30 days notice. Finally, another comment urged FDA to be "liberal and speedy in granting requests for meetings on issues that arise during the review process."

FDA declines to accept the comments. FDA will make every attempt to grant requests for meetings that involve important issues, but, due to limited resources and other demands on reviewers, will not conduct meetings on a regular basis. The agency reiterates that 90-day conferences are available "on applications for all new chemical entities and major new indications of marketed drugs" (21 CFR 314.102(c) (emphasis added)), and that end-of-review conferences are available on all applications and abbreviated applications "with priority given to applications for new chemical entities and major new indications for marketed drugs and for the first duplicates for such drugs" (21 CFR 314.102(d)). Thus, for ANDA's, 90-day conferences will generally be unavailable, and end-of-review conferences will be given low priority.

FDA adds that ANDA applicants who do request a meeting are encouraged to submit an agenda of important issues in advance for FDA's consideration. This will permit the agency to focus on specific issues and conserve resources.

Section 314.103—Dispute Resolution

FDA received no comments on this provision and has finalized it without change.

Section 314.104—Drugs with Potential for Abuse

63. Only one comment addressed proposed § 314.104, which states that FDA will inform the Drug Enforcement Administration (DEA) when an application or abbreviated application is submitted for a drug that appears to have an abuse potential. The comment supported the rule but asked FDA to "ensure the confidentiality of any information, including even the fact that an application has been submitted prior to providing that information to DEA."

Section 314.104 simply reflects FDA's obligation, under 21 U.S.C. 811(f), to forward to DEA information on any drug having a stimulant, depressant, or

hallucinogenic effect on the central nervous system if "it appears that such drug has abuse potential." (See 21 U.S.C. 811(f).) FDA's disclosure of information to another Federal agency does not necessarily result in the public disclosure of that information. (See 21 CFR 20.85.) Indeed, the regulation on public disclosure of information at § 314.430 states that FDA will not publicly disclose the existence of an application or an abbreviated application before sending the applicant an approval letter unless the application or abbreviated application's existence has been previously publicly disclosed or acknowledged (21 CFR 314.430(b)). This includes data in an application or abbreviated application (21 CFR 314.430(c)). Disclosure of any trade secret information obtained under section 505 of the act is also prohibited by section 301(j) of the act.

Section 314.105—Approval of an Application and an Abbreviated Application

64. FDA received two comments on proposed § 314.105(d). Under that provision, FDA will approve an ANDA and send the applicant an approval letter if the agency finds none of the grounds for refusing ANDA approval to apply. Both supported the rule, but one comment said an approval letter should not raise any new issues "except on the data submitted in response to an approvable letter."

With the exception of editorial matters or other minor deficiencies in an ANDA, approval letters should not raise new issues for applicants to resolve. Therefore, the comment's suggestion is unnecessary.

FDA has, on its own initiative, clarified that an approval with a delayed effective date is tentative and does not become final until the effective date. The agency has also amended § 314.105(c) to state that an abbreviated application must meet statutory standards for manufacturing and controls, labeling, and "where applicable, bioequivalence." This change reflects the statutory requirements for an ANDA.

Section 314.110—Approvable Letter to the Applicant

FDA received seven comments regarding approvable letters to applicants under proposed § 314.110. The proposed rule stated that FDA would send applicants an approvable letter "if the application or abbreviated application substantially meets the requirements of this part and the agency believes that it can approve the application or abbreviated application if

specific additional information or material is submitted or specific conditions *** are agreed to by the applicant." Proposed § 314.110(a)(1) through (a)(5) would give those submitting full or abbreviated antibiotic applications 10 days to respond to or act on an approvable letter, request a hearing, or agree to an extension of the review period. Under proposed § 314.110(b), FDA would send approvable letters to ANDA applicants only if the ANDA substantially meets FDA requirements and the agency believed that "it can approve the abbreviated application if minor deficiencies in the draft labeling are corrected and final printed labeling is submitted." The proposed rule did not give ANDA applicants a specific time period to respond to an approvable letter.

65. Two comments recommended revising proposed § 314.110(a)(3). That provision stated that an NDA applicant who receives an approvable letter may ask FDA to provide an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. One comment urged FDA to provide an opportunity for a hearing to ANDA applicants. The second comment suggested revising the rule to provide hearing dates.

With respect to ANDA applicants, FDA is amending § 314.110(b) to permit ANDA applicants to request, within 10 days after the date of an approvable letter, that FDA provide an opportunity for a hearing. This is consistent with the opportunity for a hearing provided to applicants who receive a not approvable letter under § 314.120, although the agency believes that most issues raised by approvable letters should be capable of being resolved without a hearing. The agency is also amending § 314.110(a)(3) to note that abbreviated antibiotic applications applicants will have an opportunity to request a hearing under § 314.125. The proposed rule inadvertently omitted such language even though §§ 314.101 and 314.125 suggested that these applicants had an opportunity for a hearing.

As for providing hearing dates, FDA believes that amending the rule to provide hearing dates would be impractical. FDA's experience with scheduling administrative hearings shows that finding mutually acceptable hearing dates can be difficult, and the parties often request postponements even after a hearing date has been set.

66. Two comments suggested that FDA prescribe time limits for its review of amendments submitted in response to an approvable letter. One comment

would require FDA to review an ANDA applicant's response to an approvable letter within 45 days. A second comment would require FDA to review an ANDA applicant's response within 90 days.

FDA declines to amend the rule as suggested. Under § 314.110(b), FDA will send an approvable letter to an ANDA applicant only if the ANDA meets regulatory requirements under 21 CFR part 314 and FDA "believes that it can approve the abbreviated application if minor deficiencies are corrected ***." However, FDA's ability to review an applicant's response to an approvable letter can vary due to a number of factors, such as the reviewer's skill, speed, and work load, the quality of the amendment or submission, and the complexity of the issues. Thus, the final rule does not require the agency to review an applicant's response within a single, predetermined time period. Unless the applicant's response to the approvable letter contains significant data or information requiring an extension of the review period, FDA should complete, and has the goal of completing, most of these reviews before 60 days have expired.

67. Two comments asked FDA to clarify when it would issue an approvable letter to an ANDA applicant. Under proposed § 314.110(b), FDA would send an ANDA applicant an approvable letter "only if the application substantially meets the requirements of this part and the agency believes that it can approve the abbreviated application if minor deficiencies in the draft labeling are corrected and final printed labeling is submitted." One comment said an approvable letter should be appropriate for more than minor labeling changes, and should also be used for changes such as a change in U.S.P. requirements, or the addition or deletion of an alternate analytical method. The second comment asked FDA to define the phrase, "substantially meets the requirements of this part."

FDA agrees that approvable letters may be appropriate for more than minor labeling deficiencies. Consequently, the agency has revised the rule to state that minor labeling deficiencies are simply an example of the type of deficiencies for which an approvable letter may be appropriate.

As for the phrase, "substantially meets the requirements of this part," FDA means that, with the exception of minor deficiencies, the ANDA complies with the requirements under 21 CFR part 314.

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Section 314.120—Not Approvable Letter to the Applicant

Proposed § 314.120 described the circumstances under which FDA would send a not approvable letter. Proposed § 314.120(a)(1) and (a)(2) would require applicants to amend, withdraw, or notify FDA of an intent to amend an application or abbreviated application. Proposed § 314.120(a)(3) would permit applicants to ask FDA to provide a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) or (j)(3) of the act. Applicants would be required to respond to a not approvable letter within 10 days, except that ANDA applicants, under proposed § 314.120(b), would have 180 days to respond.

68. Most comments on proposed § 314.120 recommended changes to response times. One comment suggested amending § 314.120(a) to give applicants 30 days to respond to a not approvable letter. Two comments asked that the regulation require ANDA applicants to respond to a not approvable letter within 10 days rather than the 180 days given at § 314.120(b).

FDA declines to amend the rule as suggested by the comments. The comments did not contain any justification for revising the response times, and FDA sees no reason to do so.

69. One comment asked that proposed § 314.120(a)(3) be revised to make clear that ANDA and NDA applicants, upon receipt of a not approvable letter, have the right to request that the agency provide the applicant an opportunity for a hearing.

Section 314.120(a)(3) was intended to apply to both ANDA applicants and to NDA applicants. FDA, therefore, agrees with the comment and has revised the provision accordingly. FDA has also revised § 314.120(b) to clarify that an ANDA applicant must make its request for a hearing to FDA within 10 days after the date of the not approvable letter.

Section 314.122—Submitting an Abbreviated Application for, or a 505(j)(2)(C) Petition That Relies on, a Listed Drug That is no Longer Marketed

70. One comment suggested that the title be revised to read, "Submitting an Abbreviated Application for . . ." The comment said this change would be consistent with the definitions in § 314.1

FDA agrees and has revised the title accordingly.

Section 314.125—Refusal to Approve an Application or on Abbreviated Antibiotic Application

FDA received no comments on this provision and has finalized it without substantive change.

Section 314.127—Refusal to Approve an Abbreviated New Drug Application

Proposed § 314.127 provided a list of reasons for refusing to approve an ANDA. In general, these reasons corresponded to those listed at section 505(j)(3) of the act.

71. One comment asked FDA to amend proposed § 314.127(c) to describe the type of information that it would require an ANDA applicant to submit to show that an active ingredient in an ANDA product is the same as the active ingredient in the reference listed drug. In brief, proposed § 314.127(c) would, in relevant part, have FDA refuse to approve an ANDA if there is insufficient information to show that the active ingredient(s) in the proposed drug product are the "same" as those in the reference listed drug.

Under 21 CFR 314.120, if FDA believes that an application is not approvable, it will notify the applicant in writing and describe the deficiencies in the application. Thus, in the situation described by the comment, the applicant could use the agency's written response to determine how it could demonstrate that its active ingredient is the same as that in the reference listed drug. Depending upon the circumstances, an applicant might find additional guidance in drug compendia or FDA guidelines. (See paragraph 26 above for a related comment.) The comment's suggestion, therefore, is unnecessary.

72. Proposed § 314.127(g) (now § 314.127(a)(7)) would permit FDA to refuse to approve an abbreviated application if information in the ANDA "is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers." One comment said FDA should also require ANDA holders to obtain current labeling for the listed drug every 8 months and update their own labeling accordingly.

FDA has revised § 314.150 to require ANDA holders to maintain current labeling. Failure to do so may result in withdrawal of approval. FDA will not, however, require ANDA holders to obtain current labeling or to update their own labeling every 8 months because

drug labeling does not change on a regularly scheduled basis.

73. A second comment recommended adding "or because of patent requirements" to the end of proposed § 314.127(g).

FDA agrees that a patent may be a valid reason for labeling differences between the reference listed drug and the ANDA drug product and that such differences should not be a basis for refusing to approve an ANDA. FDA has, therefore, revised the rule to indicate that labeling differences may also be due to patents or exclusivity. However, FDA cautions that it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy. For example, if the patent protects information on a new dosing regimen and FDA concludes that the preexisting dosing regimen is unsafe, the different labeling for the proposed ANDA product would be grounds for refusing to approve the ANDA.

74. Proposed § 314.127(h)(1)(i) (now § 314.127(a)(8)(i)(A)) would permit FDA to refuse to approve an ANDA if FDA had any information that the proposed drug product's inactive ingredients are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed drug product's labeling. Proposed § 314.127(h)(1)(ii) (now § 314.127(a)(8)(i)(B)) would permit FDA to refuse to approve an ANDA if the proposed drug product's composition was unsafe under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included. One comment asked FDA to merge proposed § 314.127(h)(1)(i) and (h)(1)(ii) or to explain their differences.

FDA declines to revise the rule as suggested. Section 314.127(a)(8)(i)(A) and (a)(8)(i)(B) (proposed § 314.127(h)(1)(i) and (h)(1)(ii)) reflects the statutory language at section 505(j)(3)(H)(i) and (j)(3)(H)(ii) of the act, respectively, and serves different purposes. To illustrate, if FDA concluded that an inactive ingredient in a proposed ANDA product was unsafe, it could refuse to approve the ANDA under § 314.127(a)(8)(i)(A). If the proposed ANDA product involved a combination of inactive ingredients and the combination (as opposed to each inactive ingredient), either by the type or quantity of an inactive ingredient or the manner of formulation of the inactive ingredients into the product, shows that the product was unsafe, the refusal to approve the ANDA would occur under § 314.127(a)(8)(i)(B).

FDA received four comments on proposed § 314.127(h)(2) (now § 314.127(a)(8)(ii)). Under the proposal, FDA would consider a drug product's inactive ingredients or composition to be unsafe and refuse to approve an ANDA if, on the basis of information available to FDA, "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety."

75. One comment said FDA must have a valid scientific reason, rather than a "reasonable basis" under proposed § 314.127(h)(2)(i), to conclude that an inactive ingredient raises "serious questions of safety." A second comment would replace the list of examples with a shorter, generalized list of safety questions.

If the reference to "valid scientific reason" is meant to suggest that the agency must have proof that a drug is unsafe before taking action, FDA disagrees with the comment. The preamble to the proposed rule explained how FDA concluded that section 505(j)(3)(H) of the act authorizes the agency to refuse to approve an ANDA if there is a reasonable basis to conclude that a drug product's inactive ingredients or composition raises serious questions about drug safety. In brief, section 505(e) of the act permits FDA to withdraw ANDA approval if there is evidence that the drug "is not shown to be safe." FDA can invoke this provision whenever there is a reasonable basis to conclude that a drug is unsafe even if the agency lacks proof that the drug is unsafe (54 FR 28902). In comparison, section 505(j)(3)(H) of the act authorizes FDA to refuse to approve an ANDA if "information submitted in the application or any other information available to the Secretary" shows that the drug's inactive ingredients or composition is unsafe. If FDA construed section 505(j)(3)(H) of the act as requiring proof that a drug product is unsafe before it could act, the agency would be obliged to approve an ANDA and then immediately initiate a proceeding to withdraw approval.

The U.S. Supreme Court has held that, in interpreting the stat., it must be given "'the most harmonious, comprehensive meaning possible' in light of the legislative policy and purpose," and must not "'impute to Congress a purpose to paralyze with one hand what it sought to promote with the other.'" *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 631-632 (1973) (quoting *Clark v. Uebersee Finanz-Korp.*, 332 U.S. 480, 488-489). It would be inconsistent with these

principles to interpret section 505(j)(3)(H) of the act as imposing a burden of proof on the agency that would require approval of potentially unsafe drugs, or require a greater showing that a drug is not safe to disapprove a product than is required to withdraw approval of it. Therefore, FDA is interpreting that section as authorizing disapproval of an ANDA on the same basis as withdrawal under section 505(e)(2) of the act. Thus, an ANDA may be disapproved if there is a reasonable basis to conclude that one of its inactive ingredients or its composition raise serious questions about the drug's safety.

As for deleting the list of examples of changes that raise serious questions of safety, FDA has elected to amend the last sentence in § 314.127(a)(8)(ii)(A) (proposed § 314.127(h)(2)(i)) to read, "Examples of the changes that may raise serious questions of safety include, but are not limited to, the following." This amendment shows that the list of examples is not exhaustive and that the described changes do not automatically raise serious safety concerns that preclude ANDA approval.

The proposed rule listed several examples of changes that raise serious questions of safety. These examples included the "use of a controlled release mechanism never before approved for the drug" (proposed § 314.127(h)(2)(i)(E)) and "a change in composition to include a significantly higher concentration of one or more inactive ingredients than previously used in the drug product" (proposed § 314.127(h)(2)(i)(F)).

78. The third comment asked FDA to delete § 314.127(h)(2)(i)(E) and (h)(2)(i)(F) (now § 314.127(a)(8)(ii)(A)(5) and (a)(8)(ii)(B)(6)). The comment claimed that the use of a different controlled release mechanism or a change in composition to include a significantly higher concentration of one or more inactive ingredients should not preclude ANDA approval. The comment also suggested revising § 314.127(h)(2)(i)(F) to read, "A change in composition to include levels of an inactive ingredient for which published data may exist showing such levels to be unsafe."

FDA declines to accept the comment. When read in its entirety, proposed § 314.127(h)(2) states that FDA will consider a drug's inactive ingredients or composition to be unsafe and refuse to approve an ANDA if "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety." FDA believes that such a reasonable basis

may exist in the absence of published data. As the rule and the preamble to the proposed rule note, the examples listed in proposed § 314.127(h)(2)(i)(E) and (h)(2)(i)(F) simply illustrate FDA's experience. (See 54 FR 28903.) Thus, if the proposed drug product uses a delivery or release mechanism that has never been approved for that drug or contains a higher concentration of one or more inactive ingredients, FDA will not automatically refuse to approve the ANDA. Instead, FDA will refuse to approve the ANDA only if there is a reasonable basis to conclude that the change raises serious safety questions.

FDA has, however, revised the wording in the final rule at § 314.127(a)(8)(ii)(A)(5) to replace "a controlled release mechanism" with "a delivery or a modified release mechanism." This change reflects the agency's experience with novel delivery or modified release mechanisms and places emphasis on the delivery mechanism or modified release mechanism itself whereas the proposed rule could have been interpreted as focusing concern solely on controlled release mechanisms.

FDA has also revised the final rule at § 314.127(a)(8)(ii)(A)(6) to replace "higher concentration" with "greater content." This change recognizes the fact that minutely higher concentrations of one or more inactive ingredients do not always present serious questions of safety. In contrast, a drug that has a greater content of one or more inactive ingredients often presents serious questions of safety.

77. Proposed § 314.127(h)(2)(ii) (now § 314.127(a)(8)(ii)(B)) said FDA would consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and refuse to approve the ANDA unless "it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product." A comment said that requiring information to show that changes in a preservative, buffer, or antioxidant do not affect safety was "unnecessarily excessive" because FDA knows commonly used preservatives, buffers, and antioxidants. The comment suggested revising the provision only to require submission of information on preservatives, buffers, and antioxidants that are not commonly used.

The statute authorizes the Secretary to withhold approval of an ANDA if

information submitted in the application or any other information available shows that "(i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." (See 21 U.S.C. 355(j)(3)(I f).) Thus, under the statute, the inquiry is not whether each preservative, buffer, and antioxidant is commonly used or known; instead, the inquiry is whether the preservatives, buffers, and antioxidants in the proposed drug product are safe under the conditions prescribed, recommended, or suggested in the labeling. Section 314.127(a)(8)(ii)(B) of this final rule reflects this concern, which is particularly acute for parenteral drug products. Therefore, FDA declines to revise the rule as suggested.

Section 314.150—Withdrawal of Approval of an Application or Abbreviated Application

Proposed § 314.150 concerned withdrawals of approvals of an application or abbreviated application under section 505(e) of the act. The proposed rule would permit FDA to withdraw approval of an application or abbreviated application under certain enumerated conditions, such as a finding that an imminent hazard to the public health exists (§ 314.150(a)(1)), or a finding that clinical data or other experience, tests, or scientific data show the drug is safe for use under the conditions of use approved in the application or abbreviated application (§ 314.150(a)(2)(i)).

78. Two comments said FDA should create a new provision authorizing the agency to withdraw an abbreviated application if the abbreviated application holder failed to modify its labeling to match labeling changes in the reference listed drug.

FDA agrees and has revised the rule accordingly. New § 314.150(b)(10) states that the ANDA applicant's failure to maintain drug labeling that is consistent with that of the listed drug may be grounds for withdrawing approval of the abbreviated application. The only exceptions to this withdrawal provision are labeling differences approved in the original ANDA or resulting from a patent issued on the listed drug after approval of the ANDA or from exclusivity accorded to the listed drug after approval. However, as noted in paragraph 39 above, if the agency

concludes that a labeling difference resulting from patent protection or exclusivity compromises the safety or effectiveness of the generic drug product for any remaining conditions of use, FDA may withdraw approval of the ANDA under this provision.

Section 314.151—Withdrawal of Approval of an Abbreviated New Drug Application Under Section 505(j)(5) of the Act; Section 314.152—Notice of Withdrawal of Approval of an Application or Abbreviated Application for a New Drug

79. Proposed § 314.151 (concerning withdrawals of approval of ANDA's under 21 U.S.C. 355(j)(5)) did not provide ANDA applicants the opportunity for an oral hearing in the event of a withdrawal. FDA received seven comments claiming that ANDA applicants should have an opportunity for a hearing or an oral hearing when FDA proposes to withdraw approval of an application or abbreviated application. In general, the comments argued that ANDA applicants should have the opportunity for a hearing on due process grounds or to "assure fairness." One comment stated that section 505(e) of the act authorizes hearings whenever the agency proposes to withdraw approval of an application approved under section 505, and, therefore, ANDA holders were entitled to hearings because ANDA's are authorized by section 505(j) of the act. One comment, however, would deny ANDA applicants the opportunity for a hearing because an ANDA "is completely dependent on the continued approval of the reference listed drug" and the ANDA applicant "does not take the place of the listed drug applicant for purposes of exercising the right to protect that drug."

The statute and regulations contemplate withdrawing ANDA approval under two different circumstances. First, if FDA finds the ANDA product unsafe for use, lacks substantial evidence of effectiveness under the conditions of use prescribed, recommended, or suggested in its labeling, contains an untrue statement of material fact, or meets any of the other grounds for withdrawal under section 505(e) of the act, the agency may withdraw approval "after due notice and opportunity for hearing to the applicant" (21 U.S.C. 355(e)). For ANDA products, the regulations pertaining to a withdrawal of approval under section 505(e) of the act are at § 314.150. These regulations, contrary to some of the comments' assertions, do give ANDA holders an opportunity for a hearing on a proposal to withdraw approval of an

ANDA to the extent that one or more of the grounds for withdrawal under section 505(e) of the act directly apply to the ANDA product. (See § 314.150 (a) and (b).)

The second situation in which ANDA approval may be withdrawn focuses on withdrawal of the listed drug rather than the ANDA product itself. Under section 505(j)(5) of the act, if the listed drug is withdrawn for safety or effectiveness reasons or any of the grounds listed in section 505(e) of the act, ANDA approval "shall be withdrawn or suspended . . ." The statute does not require FDA to give the ANDA holder an opportunity for a hearing before withdrawing or suspending ANDA approval.

The preamble to the proposed rule discusses this subject in greater detail. (See 54 FR 28904 through 28907.)

Notwithstanding the absence of a statutory requirement for a hearing, some comments claimed that due process requires FDA to give applicants an opportunity for an oral hearing for a proposal to withdraw ANDA approval under section 505(j)(5) of the act. FDA disagrees. As noted in the preamble to the proposed rule, courts have declared a "paper hearing" that provides adequate notice and a genuine opportunity to present one's case to be adequate. (See 54 FR 28904, July 10, 1989, and cases cited therein.) Section 314.151, therefore, gives ANDA holders a paper hearing and, if FDA cannot resolve the issues on the basis of the written submissions, permits FDA to hold a limited oral hearing. (See 21 CFR 314.151(b) and (c)(3).)

FDA believes these procedures are consistent with the statute and provide ANDA applicants adequate due process. Consequently, FDA declines to amend the rule as requested.

Section 314.153—Suspension of Approval of an Abbreviated New Drug Application; Section 314.161—Determination of Reasons for Voluntary Withdrawal of a Listed Drug

Proposed § 314.153(b) contained procedures for suspension of an ANDA when a listed drug is voluntarily withdrawn for safety or effectiveness reasons. The preamble to the proposed rule stated that "if a drug manufacturer withdraws a drug from the market which accounted for significant sales to that manufacturer, and there is no evidence to the contrary, it will be presumed that the withdrawal was for safety or effectiveness reasons" (54 FR 28907). The agency expressed its intent to employ the same presumption in applying proposed § 314.161.

80. FDA received eight comments on proposed §§ 314.153 and 314.161. All eight comments objected to the presumption stated in the preamble, but for different reasons. Many comments listed possible reasons why an NDA holder would voluntarily withdraw a drug for business or economic reasons alone. Some comments said ANDA holders should not have the burden of showing why the NDA holder voluntarily withdrew the reference listed drug. These comments would have FDA determine the reasons for a withdrawal or require the NDA holder to state its reasons for withdrawing the listed drug. Other comments said the presumption might adversely affect an NDA holder in product liability litigation. A minority of comments said the presumption's reference to "significant sales" was too vague and would produce different results between large and small firms; these comments argued that FDA, if it retained the presumption, should examine research and development expenses, percentage of a company's gross revenues, or the product's sales record for the previous year.

As stated in the preamble to the proposed rule, FDA is aware that companies may withdraw a drug from the market for reasons unrelated to the product's safety or effectiveness. (See 54 FR 28907.) The preamble also noted that FDA is not required to determine why a sponsor voluntarily withdrew a listed drug, and, considering the number of drugs withdrawn from the market every year, "it would be a needless expenditure of resources for the agency to determine the reason for each such withdrawal." Id. The comments have not raised any new issues or advanced any compelling justification for changing the presumption. The agency does note, however, that the presumption is a rebuttable one, and adds that the agency will, when the product is a top 200 drug (as reported in the April issue of *Pharmacy Times* which is based on data obtained from the National Prescription Audit conducted by IMS America, Ltd., Ambler, PA), and in other cases when it deems it to be necessary, contact the sponsor of the listed drug to inquire about the reasons for a voluntary withdrawal. In addition, the regulations do not prohibit NDA holders from disclosing their reasons for withdrawing a drug product from marketing, and FDA would consider that information in determining whether the withdrawal was for safety and effectiveness reasons. FDA would not consider the NDA holder's stated reasons for withdrawing a drug to be determinative

because such remarks could be biased. Similarly, if an ANDA applicant can show that the reasons for withdrawal of the listed drug are not relevant to the safety or effectiveness of the ANDA drug product, the agency will not suspend ANDA approval. (See 21 CFR 314.153(b)(8).)

As for the comments suggesting alternatives to "significant sales," FDA agrees that the term may have different meanings to different companies, and will adopt a case-by-case approach when determining whether a product accounted for significant sales.

For these reasons, FDA has retained the presumption without change.

Section 314.160—Approval of an Application or Abbreviated Application for Which Approval Was Previously Refused, Suspended, or Withdrawn; Section 314.162—Removal of a Drug Product from the List; Section 314.200—Notice of Opportunity for Hearing; Notice of Participation and Request for Hearing; Grant or Denial of Hearing

FDA received no comments on these provisions and has finalized them without change.

Section 314.430—Availability for Public Disclosure of Data and Information in an Application or Abbreviated Application

81. FDA received four comments on proposed § 314.430. The proposal simply added the term "abbreviated application" to FDA's preexisting public disclosure policies and did not make any substantive changes to those policies. Two comments asked FDA to release a summary basis of approval (SBA) or permit ANDA sponsors to release their own SBA's when an ANDA is approved.

Section 314.430(e)(2)(ii) permits FDA to make an SBA available for public disclosure after FDA sends an approval letter. Hence, the comment's request to have FDA release an SBA is unnecessary. FDA also declines to amend the rule to permit sponsors to release their own SBA's. The rule pertains only to the release of information by FDA; sponsors are always free to disclose whatever truthful and nonmisleading information they wish about their own products.

82. One comment asked FDA to amend the rule to reveal the "presence" of a pending ANDA without any further identification so applicants could make "a more educated decision" about possible exclusivity.

While the comment has some merit, FDA declines to amend the rule at this time. The agency is reexamining certain aspects of its public disclosure policies,

but notes that a suit to declare a patent to be invalid or not infringed by the manufacture, use, or sale of a drug product may suggest that an ANDA for that drug product has been submitted.

83. Another comment would give all NDA holders an opportunity to prevent disclosure of information for which they had previously requested confidentiality.

The act states that safety and effectiveness data submitted in an application under section 505(b) of the act and not previously disclosed to the public, "shall be made available to the public, upon request, unless extraordinary circumstances are shown." (See 21 U.S.C. 355(1).) Thus, the statute clearly favors disclosure of safety and effectiveness data except in limited situations. FDA is reexamining its policies with respect to section 505(1) of the act, and, until it completes its deliberations, declines to amend the rule as requested. FDA will continue its policy of consulting parties before disclosing information where the confidentiality of data and information is uncertain. (See, e.g., 21 CFR 20.45.)

Section 314.440—Addresses for Applications and Abbreviated Applications

FDA received no comments on this provision. However, due to reorganizations within FDA, the agency has revised the addresses to which abbreviated antibiotic application applicants and ANDA applicants are to send documents and correspondence.

Section 320.1—Definitions

Proposed § 320.1 defined "bioequivalence," in part, as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

84. Six comments argued that § 320.1 should not include nonsystemically absorbed drug products and should not provide mechanisms other than blood level tests for bioequivalence. The comments noted that section 505(j)(7) of the act states that a drug shall be considered to be bioequivalent to a listed drug if, inter alia, "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental

conditions . . ." The comments claimed that this statutory provision precludes FDA from approving ANDA's for nonsystemically absorbed drug products because, the comments argued, the rate and extent of absorption of such products cannot be measured. One comment stated that *in vivo* bioavailability studies should be done to confirm that drugs not intended to be absorbed are not unintentionally absorbed.

The agency does not agree with the comments' interpretation of the statute. In 1977, FDA issued final regulations establishing the requirements for demonstrating the bioavailability and bioequivalence of drug products approved under both full new drug applications and ANDA's (21 CFR part 320). The definitions of "bioavailability" and "bioequivalence" adopted in those regulations were, in all pertinent respects, identical to the language used in section 505(j)(7) of the act. Although the 1977 regulations and the 1984 amendments to the act, which incorporate in the statutory provision on "bioequivalence" the language of those regulations, refer to "rate and extent of absorption," the 1977 regulations explicitly applies to drugs that are not intended for systemic absorption.

As originally proposed, the regulatory definition of "bioavailability" contained explicit reference to bioavailability studies other than systemic absorption studies. In the 1977 final rule, the Commissioner of Food and Drugs removed the references to the types of studies that can demonstrate bioavailability or bioequivalence as unnecessary and placed descriptions of appropriate studies in §§ 320.23, 320.24, 320.53, and 320.57. At the same time, the Commissioner of Food and Drugs specifically rejected a comment urging the definition of bioavailability to be restricted to products absorbed into the systemic circulation, stating that the concept of bioavailability applies to all drug products. (See 42 FR 1636 at 1639; January 7, 1977.)

All drug products must be absorbed through some physical barrier to reach the site of drug action, even if that absorption involves only dispersion into a body fluid pool or entry into surface cells. It is well established that drugs may be either locally or systemically absorbed, and nothing in the language of the statute requires that the absorption result in transit through cells or to the systemic circulation. Because Congress adopted the language of the 1977 regulations, and because the legislative history contains no evidence that Congress intended to exclude

nonsystemically absorbed drugs from the coverage of the ANDA provisions of the 1984 amendments, FDA rejects the interpretation of section 505(j)(7)(B) of the act offered by these comments.

FDA also disagrees that blood levels are always appropriate or necessary measurements of bioequivalence. Bioequivalence can be established by pharmacodynamic measurement as well as by *in vitro* techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence, including the need to confirm that drugs not intended to be absorbed are not unintentionally absorbed, is determined on a case-by-case basis, depending on the drug under study.

Section 505(j)(8) of the act directs the Secretary to publish a list of all approved drugs for which ANDA's may be submitted and to state "whether *in vitro* or *in vivo* bioequivalence studies, or both such studies, are required . . ." (21 U.S.C. 355(j)(8)). *In vitro* studies are "test tube" studies intended to simulate drug effects in the human body, and are, by definition, indirect measurements of bioequivalence. Had Congress intended to require only direct measurements of the rate and extent of absorption in the human body, it would not have also permitted *in vitro* studies to satisfy the bioequivalence requirements. Thus, the statute permits and FDA's longstanding regulations provide for both indirect and direct measurements of bioequivalence applicable to nonsystemically absorbed drug products.

In summary, FDA's inclusion of nonsystemically absorbed drug products and inclusion of mechanisms other than blood level tests to establish the bioequivalence of drug products are consistent with the statute. The final rule therefore describes the types of studies that can be appropriately used to demonstrate bioavailability, and describes the bioavailability studies that are appropriate for nonsystemically absorbed drugs.

85. Proposed § 320.1(a) and (e) defined "bioavailability" and "bioequivalence" using the phrase "active ingredient or active moiety." One comment proposed that the term "active moiety," which is used in proposed § 320.1(a) and (e), does not find any statutory support and the regulations should instead use the statutory term "active ingredient." The comment's position was based on two court cases, *Abbott v. Young*, and *Ciaglo v. Quigg*, which addressed the issue of using the term "active ingredient" as provided by statute instead of using the term "active moiety," with respect to the

exclusivity provisions of title I and the patent term extension provisions of title II of the 1984 amendments, respectively. The comment stated that the courts concluded that there is a significant difference between the plain meaning of the statutory term "active ingredient" and the use of "active moiety." Equating the two is not permitted absent clear congressional intent. Thus, the comment argued that the term "active moiety" should not be used.

FDA disagrees with the comment. The court cases referred to by the comment are not relevant to FDA's use of the term "active moiety" in 21 CFR part 320. The statutory definition of "bioavailability" (section 505(j)(7)(A) of the act) uses the phrase "active ingredient or therapeutic ingredient," and the language in "bioequivalence" (section 505(j)(7)(B) of the act) uses the phrase "therapeutic ingredient." The agency is not substituting the phrase "active moiety" for the phrase "active ingredient." The phrase "active ingredient" remains in the definition of "bioavailability" in § 320.1(a) as in the statutory definition. The phrase "active ingredient" is not used in the statutory provision on "bioequivalence."

Congress clearly intended a meaning different from "active ingredient" by the term "therapeutic ingredient" or it would not have used both terms. The term "active moiety" refers to the molecule or ion in an active ingredient, excluding those appended portions of the molecule that cause the ingredient to be an ester, or a salt or other noncovalent derivative that is responsible for the physiological or pharmacological action of the ingredient. The agency believes that the term "active moiety" is more appropriate and has substituted this term for the term "therapeutic moiety" or "therapeutic ingredient" in defining the terms "bioavailability" and "bioequivalence."

86. One comment supported the proposed definition in § 320.1(e) of "bioequivalence" and opposed "across-the-board *in vivo* testing requirements." The comment asked FDA to "retain an open attitude toward the use of *in vitro* tests" and to have the regulations "reflect the fact that there are indeed other current and evolving methodologies, such as 'punch bioassays' and 'skin-blanching' tests, that will provide an equal measure of scientific comfort to demonstrate bioequivalence."

The final rule does not impose across-the-board *in vivo* testing requirements. With respect to drug products that are not included in the classes of drug

products described in § 320.22 for which the submission of evidence obtained *in vivo* is waived, FDA will consider requests for waiver of evidence obtained from *in vivo* testing on an individual basis. In addition, when other, more accurate, sensitive, and reproducible testing methods are not available, FDA will accept appropriately designed comparative clinical trials for purposes of demonstrating *in vivo* bioequivalence. Section 320.24 describes *in vivo* and *in vitro* testing approaches in descending order of accuracy, sensitivity, and reproducibility that are acceptable to FDA for determining the bioavailability or bioequivalence of a drug product.

87. The proposed definition of bioequivalence at § 320.1(e) provides that where there is an intentional difference in rate (e.g., in certain controlled release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is reflected in the proposed labeling. Is not essential to the attainment of effective body drug concentrations, and is considered medically insignificant for the drug.

One comment suggested that the last sentence in § 320.1(e) be amended by replacing the conjunction "and" with "or." The comment also suggested that FDA define an "intentional difference" as one that involves the improvement of patient compliance or the manufacture of a more pharmaceutically elegant dosage form.

FDA declines to revise the definition as suggested by the comment. The use of the conjunction "and" in the regulation is consistent with statutory language in section 505(j)(7)(B)(ii) of the act. FDA also declines to define "intentional difference" as one that involves the improvement of patient compliance or the manufacture of a more pharmaceutically elegant dosage form because there may exist other valid reasons for altering rate, for example, to reduce toxic effects produced by high concentrations of a drug in an immediate release formulation.

88. Proposed § 320.1(e) defines bioequivalence to mean the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the

same molar dose under similar conditions in an appropriately designed study. Several comments asked FDA to clarify the meaning of the phrase "significant difference" in the definition. Two comments understood "significant difference" to mean a "medically significant" or "therapeutically significant" difference. Other comments interpreted the phrase as meaning a statistically significant difference.

The determination of a significant difference requires first a judgment as to what difference in a bioequivalence parameter of interest is medically important and, second, a statistical analysis of data for the parameter to ensure that the difference determined to be important is not likely to be exceeded. Thus, based on clinical experience, the agency has developed statistical criteria for determining the bioequivalence of drug products. For example, there is a presumption that most drug products show no significant difference from the rate and extent of absorption of the listed drug and that the differences are unlikely to be clinically significant in patients when their absorption (AUC and C_{max}) is within 20 percent of the listed drug in normal subjects, and the probability that the results occurred by chance is less than 5 percent ($p < .05$).¹ In other words, unless there is a justification for different limits, the extent of absorption of the generic product must be not less than 80 percent, and not more than 120 percent, of the extent of absorption from the listed or innovator product. However, FDA will reexamine approval

¹ See "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 28–October 1, 1988," report dated January 1988 [Ref. 1]. "There was consensus at the hearing that differences of less than 20% in AUC and C_{max} between products in normal subjects are unlikely to be clinically significant in patients." Under current review procedures, the 90% confidence interval for the ratio of the test product mean AUC to that of the innovator must lie entirely within the interval (0.80, 1.20). (Page 29.)

Attachment five to the Report by the Bioequivalence Task Force states "current practice is to carry out the two one-sided tests at the .05 level of significance."

Attachment ten to the Report by the Bioequivalence Task Force states "For approval in most cases, the generic manufacturer must show that a 90% confidence interval of the difference between the mean response of its product and that of the innovator is within the limits $\pm 20\%$ of the innovator mean." FDA should use the 90% confidence interval (i.e., two one-sided t-tests each at the .05 level of significance) to evaluate the difference between treatments.

See, also, Schirrmann (Ref. 2 at p. 878), "the common $\pm 20\%$ criteria" and Nightingale and Morrison (Ref. 3 at p. 1200). "With very few exceptions, experts have concluded that differences of less than 20% in the mean AUC between brand name and generic copies are acceptable."

criteria for products falling outside the established statistical boundaries when applicants submit to FDA convincing evidence to establish a greater window of bioavailability or bioequivalence.

88. One comment asked FDA to clarify the difference between bioequivalence and therapeutic equivalence for products with intentional rate differences. Another comment argued that to rate some controlled release dosage form drugs as bioequivalent to an immediate release listed drug, but not as therapeutically equivalent, would create two subsets of bioequivalent products—one where products are therapeutically equivalent, and another where products are not therapeutically equivalent, leading to confusion in interchangeability.

Therapeutic equivalence was defined in the Federal Register of January 12, 1979 (44 FR 2932 at 2937). To be rated as therapeutically equivalent, drug products must be pharmaceutical equivalents—i.e., contain identical amounts of the same active drug ingredient in the same dosage form—and meet identical compendia or other applicable standards of identity, strength, quality, and purity; must not present a known or potential bioequivalence problem (or, if so, must meet an appropriate bioequivalence standard); must be adequately labeled; and must be manufactured in compliance with the regulations governing CDRPs. The agency will approve certain products with intentional rate differences as bioequivalent and rate them as therapeutically equivalent provided that they are pharmaceutical equivalents and the difference in rate at which the active ingredient or moiety becomes available at the site of drug action is intentional, reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug (21 CFR 320.1 (e)).

The agency believes that it is appropriate to approve certain controlled release dosage form drug products that are pharmaceutical alternatives, for which bioequivalence can be demonstrated, even though products that are not pharmaceutical equivalents cannot be rated as therapeutically equivalent. The agency's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) does not rate these products as therapeutically equivalent; thus, FDA does not consider them interchangeable. Because pharmaceutical alternatives are listed

under separate headings, and because only products rated as equivalent under the same heading are interchangeable, there should be no confusion about their interchangeability.

90. One comment disagreed that a product whose absorption rate is intentionally different from the listed drug's absorption rate can nevertheless be bioequivalent. The comment cited nitroglycerine as a product whose absorption rate is critical to effectiveness. Another comment stated that the rate differences should not need to be intentional for these products to be bioequivalent.

Both the statute and the final rule consider a product with a different rate of absorption than the listed product to be bioequivalent to the listed product only if the difference in rate is (1) intentional, (2) reflected in the labeling, (3) not essential to the attainment of effective body concentrations on chronic use, and (4) considered to be medically insignificant. All four criteria must be met for a product with a different rate of absorption to be considered bioequivalent. Thus, a product cannot be rated as bioequivalent to a listed drug when there is a difference in rate of absorption that is not intended or when the difference in rate of absorption is medically significant.

91. One comment asked that FDA expand by example or therapeutic category the drugs that can differ in rate of absorption and still be bioequivalent.

The agency is unaware of any category of products that can differ in rate of absorption and still be considered bioequivalent. Because an intentional rate difference from the reference product would need to be shown to be medically insignificant, FDA believes that determinations of bioequivalence in such cases would need to be made on a case-by-case basis.

Section 320.21—Requirements for Submission of In Vivo Bioavailability and Bioequivalence Data

Proposed § 320.21 would revise FDA's existing requirements for submitting in vivo bioavailability data to include in vivo bioequivalence data.

92. One comment stated that § 320.21(b), which would require evidence of bioequivalence to be included in an ANDA, contradicts the agency practice of accepting applications containing only bioequivalence protocols.

As stated above at paragraph 28, FDA will only accept complete applications. Incomplete applications will not be accepted. Thus, § 320.21(b) of this rule is consistent with current agency practice.

93. Proposed § 320.21(c) would require any person submitting a supplemental application to include bioavailability or bioequivalence evidence if the supplemental application proposes: (1) A change in the manufacturing process; (2) a labeling change to provide for a new indication, if clinical studies are required to support the new indication, or (3) a labeling change to provide for a new dosage regimen or an additional dosage regimen for a special patient population, if clinical studies are required to support the new or additional dosage regimen. One comment suggested that § 320.21(c)(2) and (c)(3) apply only to supplements to applications submitted under section 505(b) of the act. A second comment recommended that § 320.21(c)(2) and (c)(3) be removed because, the comment declared, bioavailability or bioequivalence data should not be needed in addition to clinical studies.

FDA disagrees with the suggested changes. The regulation at § 320.21(c)(2) and (c)(3) applies to supplements to ANDA's approved under section 505(j) of the act as well as to supplements to NDA's approved under section 505(b). (Because such a supplement to an ANDA would require review of clinical data, FDA would treat it as a submission under section 505(b) of the act.) There are a number of reasons why the agency would want bioavailability or bioequivalence data to be included in a supplement for which clinical studies were being conducted. For example, when a supplement covers a new dosage regimen, the agency is concerned about the possibility of nonlinear kinetics. Likewise, for a new patient population, the agency is concerned about the way the drug is absorbed, distributed, and cleared by the body in the target population. Some supplements for a new labeling indication will be for drug products for which a bioavailability study was never performed. In addition, clinical studies are often not done using the final formulation, and the agency may need bioavailability or bioequivalence information on the final formulation. However, in vivo bioavailability or bioequivalence studies are not always needed, and paragraphs (a)(2) and (b)(2) in § 320.21 provides for FDA to waive the requirement for in vivo studies based on the submission of adequate information.

94. Proposed § 320.21(g) would, under specific circumstances, require any person holding an approved full or abbreviated application to submit to FDA a supplemental application containing new evidence demonstrating in vivo bioavailability or

bioequivalence. One comment asked that the information that would cause FDA to require new evidence demonstrating in vivo bioavailability or bioequivalence be made publicly available and that the source of such information be disclosed.

FDA's regulations governing public information are intended to "make the fullest possible disclosure of records to the public, consistent with the rights of persons in trade secrets and confidential commercial or financial information * * * (21 CFR 20.20(a)). Publicly disclosable information includes information contained in citizen petitions as well as information submitted as part of an application under section 505(b) of the act. (See 21 CFR 10.20(j); 21 U.S.C. 355(l).) FDA will make every effort possible—consistent with its obligations to preserve certain trade secret and confidential commercial information—to make public any information it receives that would cause the agency to require new in vivo bioavailability or bioequivalence information.

95. One comment said that FDA should require retention of product samples tested for bioequivalence and that samples should be drawn from commercial-sized lots produced on the equipment that will be used to manufacture the marketed product.

FDA agrees in part with the comment. In the Federal Register of November 8, 1990 (55 FR 47034), FDA published an interim rule that requires retention of bioavailability and bioequivalence testing samples. The interim rule applies to manufacturers who conduct in-house bioavailability and bioequivalence tests and to facilities conducting such testing under contract for a drug manufacturer. FDA does not agree that bioequivalence studies need necessarily be conducted on commercial-sized lots if certain conditions are met. See Office of Generic Drugs Policy and Procedure Guide 22-90 (September 13, 1990).

Section 320.22—Criteria for Waiver of Evidence of In Vivo Bioavailability or Bioequivalence

Proposed § 320.22 would, among other things, revise the existing criteria for waiving evidence of in vivo bioavailability to include waivers of in vivo bioequivalence, delete automatic waivers of in vivo bioavailability for certain drug products, and remove the list of "bioproblem" drugs.

96. One comment argued that the statute prohibits a waiver of in vivo bioequivalence data. Another comment urged that § 320.22 be revised to waive in vivo bioequivalence requirements for

topically applied preparations and drug products that are oral dosage forms not intended to be absorbed.

Although the statute requires ANDA applicants to provide bioequivalence information (except where the ANDA is being submitted for a change in a listed drug for which a suitability petition has been granted), it does not require that bioequivalence be shown through in vivo methods. For example, section 505(j)(8)(A)(i)(III) of the act requires the Secretary to publish and make available to the public "whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications . . ." If ANDA applicants were limited to in vivo bioequivalence methods, the statutory reference to in vitro methods would be superfluous. FDA, therefore, disagrees with the comment that the statute prohibits waivers of in vivo methods for demonstrating bioequivalence.

FDA has removed the automatic waiver of evidence of in vivo bioavailability for topically applied preparations and oral dosage forms not intended to be absorbed because the agency believes in vivo bioavailability may be required for certain products. Variations in the manufacturing process used by each individual manufacturer may result in differences in the bioavailability of these drug products. While neither topical drug products nor oral dosage forms not intended to be absorbed are listed in the class of products whose bioavailability may be considered self-evident based on other data in the application, applicants of such products may nevertheless request a waiver of the requirements for in vivo data under § 320.22(a). The agency will review each product on a case-by-case basis to determine if an in vivo study is necessary.

97. One comment said the proposed rule would increase duplicative safety and efficacy tests and increase the time and expense of obtaining ANDA's by reverting to "across-the-board" in vivo study requirements. It argued that removing automatic waivers for topical and nonsystemically absorbed drugs would make it nearly impossible for an ANDA applicant to obtain marketing approval and impose new bioavailability standards that exceed the pioneer's testing requirements.

Although § 320.22, as revised, removes the automatic waiver for topical and nonsystemically absorbed oral dosage products, this change does not require applicants to submit evidence of in vivo bioavailability or in vivo bioequivalence in every case. The elimination of the automatic waiver for nonsystemically absorbed oral dosage products simply

reflects FDA's view that requests for waiver of in vivo bioavailability and bioequivalence for these products need to be reviewed on a case-by-case basis. While the amendments may well increase the number of in vivo studies required, the regulation does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo bioavailability or bioequivalence data provided the product meets the criteria in § 320.22.

FDA concedes that the burden of showing bioequivalence may sometimes be comparable to, or perhaps even greater than, the pioneer's burden of showing bioavailability. In such cases, FDA believes that the additional data are needed to meet current standards for bioequivalence. FDA also notes that the generic company's burden is not likely to be nearly as great as the pioneer's burden of showing that a drug product is safe and effective for its proposed uses.

98. Under proposed § 320.22(b)(1), FDA would waive the requirement for submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of drug products that are solutions for intravenous administration. The proposal stated that the in vivo bioavailability or bioequivalence of these drug products is "self-evident" provided that the drug products contain the same active and inactive ingredients in the same concentration as the listed drug product (21 CFR 320.22(b)(1)(ii)). Proposed § 320.22(c) would provide for a waiver of in vivo data requirement for those "parenteral drug products that are determined to be DESI-effective or that are shown to be identical in both active and inactive ingredient formulation" to a drug product that is currently approved in an NDA (provided that the drug is neither in suspension form, nor phenytoin sodium powder).

On its own initiative, FDA is revising § 320.22(b)(1)(i) to include solutions for all parenteral injections within its scope. As revised, the provision includes, among others, intraocular, intravenous, subcutaneous, intramuscular, intra-arterial, intrathecal, intrasternal, and intraperitoneal solutions intended for parenteral injection. The in vivo bioavailability or bioequivalence of any drug product in that class may be shown without in vivo data if the product contains the same active and inactive ingredients in the same concentration as a drug product that is a subject of an approved full new drug application. Because all parenteral solutions are now included at § 320.22(b)(1)(i), the agency has deleted § 320.22(c), which is no longer needed.

99. Proposed § 320.22(b)(3) would waive the requirement for submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of a product that is an oral solution, elixir, syrup, tincture, or similar other solubilized form provided that it contains: (1) An active ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and (2) no inactive ingredient that may significantly affect absorption of the active ingredient or active moiety. One comment asked that ophthalmic and otic solutions be added to the class of products described in § 320.22(b)(3) whose bioavailability or bioequivalence is deemed self-evident.

Although FDA does not believe that the in vivo bioavailability or bioequivalence of otic and ophthalmic solutions can be considered self-evident based on compliance with the criteria described in § 320.22(b)(3), FDA does believe that it can assume the bioavailability or bioequivalence of an ophthalmic or otic product, if the product meets the criteria described in § 320.22(b)(1)(ii), i.e., the product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. The regulation is revised accordingly.

100. Two comments objected to the requirement in § 320.22(b)(1)(ii) that inactive ingredients be the same as those in the listed drug, arguing that some differences should be allowed and that ANDA applicants do not know the inactive ingredients in the listed drug.

FDA declines to accept the comment. The final rule requires drug products intended for parenteral injection to contain the same inactive ingredients in the same concentrations to obtain a waiver from the in vivo bioavailability or bioequivalence requirement because FDA cannot always predict the consequences of minor changes (e.g., in salt concentration). FDA believes this criterion is important to retain even when the necessary information is not freely available to ANDA applicants. FDA notes that under 21 CFR 201.100(b)(5) drug products for other than oral use must usually list the names of all inactive ingredients except flavorings, perfumes, and color additives. In addition, under 21 CFR 201.100(b)(5)(ii), a drug product, "if it is intended for administration by parenteral injection, (must list) the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name."

and a statement of their effect * * *. Thus, ANDA applicants should be able to determine the identity of inactive ingredients for all nonoral dosage forms and the quantity or proportion of inactive ingredients for many drug products, including all parenterals. In many other cases, the identity and quantity of inactive ingredients will be voluntarily disclosed on the listed drug's label or otherwise ascertainable.

101. Proposed § 320.22(b)(3)(i) stated the conditions under which the bioavailability or bioequivalence of oral solutions, elixirs, syrups, tinctures, or similar products could be considered self-evident. One comment asked that § 320.22(b)(3)(i) be revised to include solutions for application to the skin.

The agency agrees that the in vivo bioavailability or bioequivalence of a solution for application to the skin may be considered self-evident, provided that it has the same active ingredients in the same concentration as the listed drug and no inactive ingredient or change in formulation that may significantly affect absorption of the active drug ingredient or active moiety. Therefore, the regulation at § 320.22(b)(3)(i) has been revised to include solutions for application to the skin. On its own initiative, FDA is revising § 320.22(b)(3)(iii) to make clear that the waiver in that section is conditioned on the applicant making no change in product formulation, including deletion of an inactive ingredient, that may significantly affect the absorption of the active drug ingredient or active moiety.

102. Existing § 320.22(d)(5) waives the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of a drug product if the product contains the same active drug ingredient and is in the same strength and dosage form as a drug product that is the subject of an approved full or abbreviated new drug application, and both products meet an appropriate in vitro test. FDA proposed to remove this provision, stating that there was no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence. Three comments asked that existing § 320.22(d)(5) be retained. One comment contended that FDA had little evidence to show that in vitro data alone are not sufficient for the same product manufactured by the same sponsor.

FDA rejects these comments. The burden of showing that a new product is bioavailable or bioequivalent rests with the applicant. In general, the submission of in vivo data is required to support a new product unless there is a known in vivo/in vitro correlation, in which case

in vitro data alone may be sufficient. Section 320.22(d) of this final rule lists certain classes of drug products whose bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo. (In addition, FDA continues to waive in vivo data for certain drugs determined to be effective for at least one indication under the DESI program.) As FDA has no evidence to show that in vitro data alone are regularly sufficient to support the bioequivalence of any other drug classes, the agency believes that it is inappropriate to retain existing § 320.22(d)(5). Section 320.22(d)(5) is, therefore, removed.

103. One comment urged that existing § 320.22(d)(5) be retained as a mechanism for waiving in vivo data requirements for minor formulation changes, i.e., changes in colors or flavor. The comment stated that some FDA review divisions require new applications for products that contain a new flavor or color, and concluded that these newly formulated products are not eligible for the waivers described in proposed § 320.22(e)(4).

The comment is incorrect in assuming that products that are reformulated to contain a new flavor, color, or preservatives are ineligible for waiver under proposed § 320.22(e)(4) (§ 320.22(d)(4) in this final rule). Such new formulations are eligible for waiver whether they are covered by a new application or by a supplement to an approved application.

104. Proposed § 320.22(e)(2) (§ 320.22(d)(2) in this final rule) would waive the requirement for the submission of in vivo bioavailability evidence if the drug product "is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval" and the bioavailability of the other drug product has been demonstrated, both drug products meet an appropriate in vitro test approved by FDA, and the applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients. One comment suggested that the agency revise § 320.22(e)(2) to include all dosage forms, including extended release dosage forms. A second comment asked FDA to extend the waiver to extended release capsules whose active ingredients are beaded materials.

The agency never intended to include extended release dosage forms, and has modified § 320.22(d)(2) to so state. The agency disagrees that it would be appropriate to grant waivers to all

extended release dosage forms or to all extended release capsules whose active ingredients are beaded materials because the current state of science and technology does not always permit meaningful correlations between in vitro dissolution rates and the rate and extent of in vivo bioavailability for these products. FDA believes that waivers may be appropriate under some circumstances for certain beaded extended release dosage forms. Waivers are ordinarily granted for certain beaded dosage forms, where bioavailability has already been established and the only difference between the reference product and the drug under study is not in the type of bead, but in the quantity of beads. However, waivers will not be granted for beaded dosage forms with nonlinear kinetics because differences of minor therapeutic consequence at lower dose could become greatly exaggerated at higher doses. FDA will consider waiver requests for such products on an individual basis.

105. Proposed § 320.22(g) would permit FDA to require in vivo bioavailability or bioequivalence data if it determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product. One comment asked that § 320.22(g) not be used unfairly by pioneer companies to remove generic applicants from the market by bombarding the agency with small bioequivalence changes.

This provision, renumbered § 320.22(f), if not intended and would not be implemented to give unfair marketing advantage to any particular manufacturers. Rather, it permits FDA to impose additional requirements to ensure the continued bioavailability or bioequivalence of a drug product.

Section 320.23—Basis for Demonstrating in Vivo Bioavailability or Bioequivalence

The proposed amendments to § 320.23 would, among other things: (1) Permit applicants whose drug products are not intended to be absorbed into the bloodstream to demonstrate bioavailability by measuring the rate and extent to which the active ingredient or active moiety was absorbed and became available at the site of drug action (§ 320.23(a)(1)); (2) state that statistical techniques used shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability (§ 320.23(a)(2)); (3) rephrase the conditions under which a drug product whose rate of absorption

differs from the reference listed drug can be considered bioavailable (§ 320.23(a)(3)); and (4) declare two drug products to be bioequivalent if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple doses (§ 320.23(b)).

106. One comment stated that proposed language in § 320.23(a)(2) on "differences in rate * * * of absorption" is ambiguous. The comment said the phrase could be interpreted to mean either differences in the "first-order micro-rate constant for absorption," or, alternatively, maximum concentration, C_{max} , and time to maximum concentration, T_{max} .

The comment correctly points out that the regulation does not specify how absorption rate should be measured. Because drug product parameters may vary, absorption parameters are determined based on the nature of the drug being evaluated.

Section 320.24—Types of Evidence to Establish Bioavailability or Bioequivalence

107. One comment asked that § 320.24 require that an applicant submitting an ANDA for a drug that has a significant difference in a pharmacodynamic parameter that is correlated with safety or therapeutic effect demonstrate that the difference is not clinically significant. The comment also asked that § 320.24 be revised to state FDA's willingness to accept in support of an ANDA pharmacodynamic evidence in lieu of pharmacokinetic profiles when one or more pharmacodynamic parameters correlate with a drug's therapeutic effect.

The ANDA process is intended to provide a rapid and efficient route for generic drug approval. Section 505(j)(7) of the act requires that FDA find a generic drug product to be bioequivalent to the reference listed drug if differences in their rates and extents of drug absorption fall within predetermined statistical limits.

Standards for determining bioequivalence for a product are intended to reflect the nature of the therapeutic response for that product. Once the therapeutic index has been determined, the equivalence of a product's therapeutic response can be measured via plasma drug concentrations, which are generally believed to provide a precise and accurate reflection of product performance. It is highly unlikely that a

clinically significant difference in product safety and efficacy will exist for a product that meets an applicable bioequivalence standard. However, should postmarketing surveillance or other information suggest the possibility of therapeutic inequivalence, the approval criteria for that drug entity would be reevaluated.

In general, for systemically absorbed drugs, blood level profiles are a more sensitive index of rate and extent of drug delivery than pharmacodynamic measures. Therefore, except for cases where the agency has indicated otherwise, when blood levels of a drug are measurable, product bioavailability and bioequivalence will be based on pharmacokinetic rather than pharmacodynamic response.

108. Proposed § 320.24(a) stated that applicants should conduct bioavailability or bioequivalence studies "using the most accurate, sensitive, and reproducible approach * * *." One comment suggested that proposed § 320.24(a) be revised to state that applicants who have begun bioequivalence testing under an FDA guidance document would not have to recommence their studies if FDA's guidance changes in the interim.

FDA declined to adopt the comment. Generally, the agency will not ask an applicant to recommence a study that is conducted under an FDA guidance document. However, if new information suggests the need to reconsider agency guidance on study design, the agency will not be bound by that previous guidance. Therefore, under some important circumstances, it may be necessary for an applicant to recommence a study.

109. Proposed § 320.24(b) lists tests in descending order of accuracy, sensitivity, and reproducibility that are acceptable approaches for establishing the bioavailability and bioequivalence of a drug product. On its own initiative, the agency has added to the list of acceptable tests "currently available in vitro tests that ensure human in vivo bioavailability." The addition is intended for drug products determined to be effective under DESI for at least one indication that contain no active ingredients regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. These products are coded "AA" in the list of "Approved Drug Products with Therapeutic Equivalence Evaluations." The agency has created new § 320.24(b)(5) to list these in vitro tests, and has renumbered proposed § 320.24(b)(5) as § 320.24(b)(6).

110. One comment questioned whether the three tests listed in

§ 320.24(b)(1) are themselves listed in descending order of accuracy, sensitivity, and reproducibility. The comment suggested that FDA renumber the approaches to make clear its intent.

The approaches in § 320.24(b)(1) are listed in descending order of accuracy, sensitivity, and reproducibility. This means that the approach under § 320.24(b)(1), is preferable to § 320.24(b)(1)(ii), as the comment suggested. The agency believes the regulatory language clearly captures the agency's intent, and does not believe that renumbering the approaches is needed. The comment is therefore rejected.

111. Under proposed § 320.24(b)(1), one approach for demonstrating bioavailability or bioequivalence would be through "an in vivo test in humans in which the concentration of the active ingredient or active moiety and its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time." One comment contended that measurement of active metabolites in an in vivo test should be the exception rather than the rule, and that measurement of metabolites should not be required where the activity of the metabolite is not well documented.

In general, the determination of whether a metabolite would be used in the assessment of a product's bioavailability or bioequivalence is dependent upon the pharmacokinetic characteristics of the drug (e.g., product input function, rate of metabolite formation, and half-lives of the various species). Section 320.24(b) has been revised to make clear that measurement of active metabolites will only be required when appropriate.

112. Two comments objected to the inclusion in the list of approaches to demonstrate the bioavailability or bioequivalence of a product of "well-controlled clinical trials that establish the safety and effectiveness of the product" (§ 320.24(b)(4)). The comments argued that clinical efficacy or safety trials to demonstrate bioequivalence are not bioequivalence determinations under the statute. The comments suggested that FDA should treat as § 505(b) application any ANDA application whose bioequivalency is based on clinical safety and effectiveness data.

As stated elsewhere in this document, the statute does not restrict applicants to a specific method for demonstrating bioequivalence. The preexisting regulations at 21 CFR 320.57 permitted applicants to demonstrate bioavailability and bioequivalence

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through well-controlled clinical trials. The final rule retains this provision in § 320.24(b)(4). The measurement of clinical endpoints may thus be an acceptable approach for establishing bioequivalence for purposes of ANDA approval. The fact that clinical trial data are submitted to demonstrate bioequivalence does not therefore force FDA to convert an application to a section 505(b) application.

113. Proposed § 320.24(b)(4) would permit an applicant to determine a product's in vivo bioavailability or bioequivalence through well-controlled clinical trials or comparative clinical trials provided that analytical methods "cannot be developed" to determine that product's bioavailability or bioequivalence through the tests listed in proposed § 320.24(b)(1), (b)(2), or (b)(3). The comment urged that FDA replace the phrase "cannot be developed" with "have not been developed."

The agency declines to accept the comment because it believes that well-controlled clinical trials or comparative clinical trials should be used only when analytical methods cannot be developed using current technology. To allow clinical trials when such methods have not been developed would encourage their use in situations where technology exists, but an applicant prefers not to develop the analytical methods.

Section 320.30—Inquiries to FDA and FDA Review of Protocols

Proposed § 320.30 strongly recommends that persons planning to conduct a bioavailability or bioequivalence study submit proposed protocols to FDA for review before conducting the study. The proposed regulation also provided addresses for general inquiries on in vivo bioavailability and bioequivalence requirements.

114. Two comments suggest that the regulation be revised to require FDA to review proposed protocols. Two other comments asked that, to ensure timely review, the regulation specify a time period in which FDA must respond to requests for review of a protocol.

The agency will review proposed protocols as expeditiously as its resources and other agency demands permit. However, due to limited resources and an inability to predict the volume of submissions it will receive, the agency cannot commit itself to reviewing regularly all protocols nor will FDA specify a time limit for conducting reviews.

115. Proposed § 320.30(b)(2) would have FDA offer advice with respect to whether the reference material to be

used in a proposed bioavailability or bioequivalence protocol is appropriate. One comment asked that, when there are two approved innovator products that are not bioequivalent to each other, FDA allow either to be the reference standard.

As noted in the preamble to the proposed rules (54 FR 28872 at 28880), FDA intends to select reference listed drugs, which will be the reference standards for bioequivalence determinations. FDA will identify in future editions of the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" the reference listed drug. By designating a single reference listed drug against which all generic versions must be shown to be bioequivalent, FDA hopes to avoid significant variations among generically equivalent drug products. Also, as stated previously, if an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

Section 320.31—Applicability of Requirements Regarding on "Investigational New Drug Application"

Proposed § 320.31 listed the types of bioavailability and bioequivalence studies for which an investigational new drug application (IND) would be required. Proposed § 320.31(a)(3) would require an IND if the in vivo bioavailability or bioequivalence study involved a cytotoxic drug product.

116. Two comments asked FDA to justify requiring IND's for cytotoxic products and for multiple-dose studies on controlled release products when no single-dose studies have been completed.

FDA believes that IND's are appropriate in these cases because of the potential risks to study participants through dose dumping or other toxic effects. FDA has 30 days to review and respond to an IND to determine potential safety problems and to assure effects that could threaten the safety of the subject participating in the study.

Section 320.51—Procedures for Establishing or Amending a Bioequivalence Requirement

117. The proposed rule proposed to remove 21 CFR 320.51, which sets forth procedures for establishing or amending a bioequivalence requirement. One comment asked that § 320.51 not be removed because it requires FDA to use notice and comment rulemaking to develop or amend a bioequivalence requirement.

Because the 1984 amendments require that any new generic drug products be

demonstrated to be bioequivalent to the reference listed drug (unless it is the subject of an approved ANDA suitability petition), additional authority to impose bioequivalence requirements with respect to such products is not needed. However, on its own initiative, the agency has decided not to remove § 320.51 because it establishes a procedure to impose bioequivalence requirements on other classes of drug products not covered by the bioequivalence requirements in the 1984 amendments, including drug products not subject to premarket approval and drug products whose new drug status is not yet determined. In this final rule, § 320.51 has been redesignated and revised as § 320.32.

IV. Economic Assessment

FDA has considered the economic impact of this regulation which clarifies and facilitates the implementation of Public Law 98-417. Title I of Public Law 98-417 eliminated unnecessary regulatory barriers for generic drug products and has resulted in generic competition on many important post-1962 drugs. Generic drug sales account for a significant portion of total prescription drug sales, and many of these sales would not have occurred in the absence of Public Law 98-417.

Prior to the implementation of title I of Public Law 98-417, in order to market a generic post-1962 drug product, drug sponsors were required to duplicate the innovator's safety and efficacy testing and to submit a "duplicate" NDA. Under title I, sponsors no longer incur duplicate testing costs and are able to market generic products after submitting and gaining approval for an ANDA which does not include the duplicate testing requirement. The costs associated with preparing and submitting an ANDA are significantly lower than the costs for submitting duplicate NDAs for the same products.

The benefits of these implementing regulations for title I are twofold: (1) savings to consumers who purchase generic post-1962 prescription drug products, and (2) savings to sponsors of generic drug products who submit ANDA's to the agency in order to gain approval to market their products. The consumer savings are the result of the increased availability of lower-priced generic drug products. As new generic products are made available annually (as their patents expire and generic drug products enter the marketplace) the savings to consumers should reach several billion dollars annually over the next 5 to 10 years. The savings to sponsors will vary depending on the

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number of applications submitted annually. Small businesses will also be favorably affected because the barriers to market entry have been lowered thereby allowing these firms to enter the generic drug market without incurring duplicate safety and efficacy testing costs. Consequently, FDA concludes the benefits of these regulations implementing title I far exceed the costs. FDA also believes it has streamlined the ANDA process as much as possible thus minimizing the costs and maximizing the net benefits.

The regulatory framework for processing ANDA's under section 505(j) of the act has been in existence since the enactment of the Drug Price Competition and Patent Term Restoration Act in 1984. Thus, most required procedures and their associated economic consequences have been in effect since that time. This rule simply clarifies and facilitates the implementation of the act and will not affect the pace or magnitude of these impacts. Therefore, FDA concludes that this rule is not a "major rule" as defined

by Executive Order 12291 and does not require a regulatory impact analysis. Similarly, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities, and therefore does not require a regulatory flexibility analysis under the Regulatory Flexibility Act of 1980 (Pub. L. 96-354).

V. Environmental Impact

The agency has determined under 21 CFR 25.24(e)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1980

This final rule contains information collections which have been submitted for approval to the Office of Management and Budget under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection

are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Abbreviated New Drug Application Regulations.

Description: The information requirements collect information from persons who must obtain FDA approval prior to marketing generic copies of previously approved drugs. These persons must submit information in the form of applications, notices, and certifications. FDA will use the information submitted to determine whether the proposed generic drug is eligible for consideration, under what provisions an application would be considered, and whether the proposed drug is identical to the pioneer drug it purports to copy.

Description of Respondents:
Businesses.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Section	Annual number of respondents	Annual frequency	Average burden per response	Annual burden hours
314.50(g)	1	1	1 hour.....	1
314.50(j)	8	1	2 hours.....	16
314.50(l)	50	1	2 hours.....	100
314.54	10	1	80 hours.....	800
314.80, 310.305	40	1	8 hours.....	320
314.81	700	1	10 min.....	119
314.83	82	1	10 hours.....	820
314.94	850	1	160 hours.....	136,000
314.110	10	1	40 hours.....	400
314.122, 314.161	1	1	10 hours.....	10
Total.....				138,586

There were no comments received on the Paperwork Reduction Act clearance submission or on the burden estimates. Therefore, no changes have been made to these burden estimates. However, the final rule does not finalize the provisions of the proposed rule on patent certification and market exclusivity. The agency has not included those estimates in the final rule.

VII. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the

Food and Drug Administration, September 29–October 1, 1988," January 1988.

2. Schuirmann, D. J., "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability," Journal of Pharmacokinetics and Biopharmaceutics, 15(6):657, 1987.

3. Nightingale, S., and J. Morrison, "Generic Drugs and the Prescribing Physician," Journal of the American Medical Association, 270(9):1200, 1997.

4. Skelt, J. P. et al., "Workshop Report: In Vitro and In Vivo Testing and Correlations for Oral Controlled/Modified-Release Dosage Forms," Pharmaceutical Research, 7:975–982, 1990.

List of Subjects

21 CFR Part 2

Administrative practice and procedure, Cosmetics, Drugs, Foods,

21 CFR Part 5

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

EXHIBIT C

Guidance for Industry

Changes to an Approved NDA or ANDA

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
November 1999
CMC**

Guidance for Industry

Changes to an Approved NDA or ANDA

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*Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
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**U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY¹

Changes to an Approved NDA or ANDA

I. INTRODUCTION

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act).² Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

The purpose of this guidance is to provide recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with Section 506A. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) package, (6) labeling, (7) miscellaneous changes, and (8) multiple related changes.

Recommendations on reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by CDER are found in the guidance for industry entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).³

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product

¹ This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on how it will apply the requirements of section 506A of the Act for NDA and ANDA products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

² Pub. L. 105-115.

³ FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

as they may relate to the safety or effectiveness of the product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.⁴

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on *reporting categories* in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act provides for two types of changes being effected supplements (see section II) while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes being effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.

If guidance for either recommended filing categories and/or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

II. REPORTING CATEGORIES

Section 506A of the Act provides for four reporting categories that are distinguished in the following paragraphs.

A *major change* is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product (506A(c)(2)). A major change requires the submission of a supplement and approval by FDA prior to distribution of the product made using the change (506A(c)(1)). This type of supplement is called, and should be clearly labeled, a *Prior Approval Supplement*. An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a *Prior Approval Supplement — Expedited Review Requested*.⁵ Requests for expedited review based on extraordinary hardship should

⁴ A list of CDER guidances is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

⁵ Internal Agency policies and procedures relating to processing requests for expedited review of supplements to approved ANDAs and NDAs are documented in CDER's Manual of Policies and Procedures (MAPP) at 5240.1 and 5310.3, respectively. MAPPs can be located on the Internet at

be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A *moderate change* is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the product made using the change (506A(d)(3)(B)(i)). This type of supplement is called, and should be clearly labeled, a *Supplement — Changes Being Effected in 30 Days*. The product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (506A(d)(3)(B)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended with the missing information.

FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (506A(d)(3)(B)(ii)). This type of supplement is called, and should be clearly labeled, a *Supplement — Changes Being Effected*. If, after review, FDA disapproves a changes being effected in 30 days supplement or changes being effected supplement, FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (506A(d)(3)(B)(iii)).

A *minor change* is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next *Annual Report* (506A(d)(1)(A) and (d)(2)).

An applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol should be submitted as a prior approval supplement, if not approved as part of the original application. FDA intends to issue separate guidance on comparability protocols.

III. GENERAL REQUIREMENTS

<http://www.fda.gov/cder/mapp.htm>.

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (506A(a)).

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the *Code of Federal Regulations* (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

A changes being effected supplement for labeling changes must include 12 copies of the final printed labeling (21 CFR 314.50(e)(2)(ii)).

Except for a supplemental application providing for a change in labeling, an applicant should include a statement in a supplemental application or amendment certifying that the required field copy (21 CFR 314.50) of the supplement or amendment has been provided.⁶

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates (i.e., assesses) the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product (506A(b)).⁷ For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b), (c)(1), (d)(2)(A), and (d)(3)(A)). Recommendations on the type of

⁶ Mailing information for field copies is provided in 21 CFR 314.440(a)(4). FDA recommends that the *applicant's home FDA district office* referred to in the regulations be the district office where the applicant's headquarters is located.

⁷ *Validate the effects of the change* means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug. The term *assess* or *assessment*, as used in this guidance, is not the same as CGMP validation. Unless otherwise specified by FDA, CGMP validation (e.g., process, equipment) data need not be filed in the application but should be retained at the facility and be available for review by FDA at the Agency's discretion. For example, in addition to the information assessing the effects of the change specified in 506A(b) of the Act, validation information on sterilization processes should be submitted in an NDA or ANDA.

information that should be included in a supplemental application or annual report is available in guidance documents. If no guidance is available on the type of information that should be submitted to support a change, the applicant is encouraged to contact the appropriate chemistry or microbiology review staff.

1. Conformance to Specifications

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.⁸ A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirmation that the material affected by manufacturing changes continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the product. For example:

- Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously

⁸ If a specification needs to be revised as a result of the change, this would be considered a multiple change (See sections VIII and XII).

qualified level.⁹

- Evaluation of the hardness or friability of a tablet after certain changes.
- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the product made after the change equivalent to the product made before the change? An exception to this general approach is that when bioequivalence should be redocumented for certain ANDA postapproval changes, the comparator should be the reference listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, *equivalent* does not necessarily mean *identical*. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, **the change should be filed in a prior approval supplement,**

⁹ Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances (e.g., ICH Q3B *Impurities in New Drug Products* (November 1996)).

regardless of the recommended reporting category for the change. For example, a type of process change with a recommended filing category of a supplement — changes being effected in 30 days, could cause a new degradant to be formed that requires qualification and/or identification.¹⁰ However, the applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the product as it may relate to the safety or effectiveness of the product.

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (506A(c)(2)(A)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a changes being effected supplement or annual report is not included in this document because of the complexity of these recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES¹¹

A. General Considerations

CDER should be notified about a change to a different manufacturing site used by an applicant to (1) manufacture or process drug products,¹² in-process materials, drug substances, or drug

¹⁰ Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances.

¹¹ See Attachment A for a discussion of the definition of *same manufacturing site* and *different manufacturing site*.

¹² Manufacturing or processing drug product would also include the preparation (e.g., sterilization, depyrogenation, irradiation, washing) by the applicant or applicant's contractor of container closure systems or packaging components.

substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. The supplement or annual report should identify whether the proposed manufacturing site is an alternative or replacement to those provided for in the approved application.

A move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, should be filed as a prior approval supplement if the site does not have a *satisfactory CGMP inspection*¹³ for the *type of operation*¹⁴ being moved (see sections VI.B.1 and 2).

For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations, the potential for adverse impact and, consequently, the recommended reporting category depends on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.

Except for those situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, moving production operations between buildings at the same manufacturing site or within a building, or construction activities occurring at a manufacturing site, do not have to be reported to CDER.

A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

¹³ See Glossary for a definition of *satisfactory CGMP inspection*.

¹⁴ See Attachment B for a discussion of the term *type of operation*.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.
2. A move to a different manufacturing site, except those used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.
3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,¹⁵ transdermal systems, liposomal products, depot products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.
4. Transfer of manufacturing of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved products. For example, transferring the manufacture of a lyophilized product to an existing aseptic process area where no approved lyophilized products are manufactured or the approved lyophilized products being manufactured have dissimilar container types and/or sizes to the product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.

¹⁵ Certain operations relating to the manufacture, processing, or primary packaging of modified-release solid oral dosage form products need not be reported in a prior approval supplement (see sections VI.C.1.c and VI.D.6).

5. Transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a supplement — changes being effected in 30 days (see section VI.C.1.a).

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a prior approval supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2).

1. Supplement — Changes Being Effected in 30 Days

- a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.
- b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site, except as provided for in section VI.B.4.
- c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form products.
- d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing.

2. Supplement — Changes Being Effected

- a. A move to a different manufacturing site for the manufacture or processing of the final intermediate.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a prior approval supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging.
2. A move to a different manufacturing site for labeling.
3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate.
4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application and the facility has a satisfactory CGMP inspection for the type of operation being performed.
5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.
6. A move to a different manufacturing site for the ink imprinting of solid oral dosage form products.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product.

In some cases there may be a substantial potential for adverse effect, regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change should be filed in a prior approval supplement.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.
2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:
 - Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
 - Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
 - Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).
 - Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
 - Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be filed as a Supplement — changes being effected in 30 days.
 - Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process

time.

- Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.
- Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.
- Changes in sterilizer load configurations that are outside the range of previously validated loads.
- Changes in materials or pore size rating of filters used in aseptic processing.

3. The following changes for a natural product:¹⁶

- Changes in the virus or adventitious agent removal or inactivation methods. This is applicable to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.
- For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.
- For drug substance and drug product, establishment of a new master cell bank or seed.

4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant. For example:

a. Drug product

- Dry to wet granulation or vice versa.
- Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).

b. Drug substance

- Filtration to centrifugation or vice versa.
- Change in the route of synthesis of a drug substance.

5. The following changes for drug substance

¹⁶ For the purposes of this guidance, *natural product* refers to materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

- Any process change made after the final intermediate processing step in drug substance manufacture.
- Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.

6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on *CDER-approved products*.¹⁷
7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. *Supplement — Changes Being Effected in 30 Days*
 - a. For drug products, any change in the process, process parameters and/or equipment, except as otherwise provided for in this guidance.
 - b. For drug substances, any change in process and/or process parameters, except as otherwise provided for in this guidance.
 - c. For natural protein drug substances and drug products:
 - Any change in the process, process parameters, and/or equipment, except as otherwise provided for in this guidance.
 - An increase or decrease in production scale during finishing steps that involves new or different equipment.
 - Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.
 - d. For sterile products, drug substances, and components, as appropriate:

¹⁷ See Attachment C for a discussion of *CDER-approved*.

- Changes in dry heat depyrogenation processes for glass container systems for products that are produced by terminal sterilization processes or aseptic processing.
- Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) that require additional validation studies for the new parameters.
- Filtration process changes that provide for a change from single to dual product sterilizing filters in series, or for repeated filtration of a bulk.
- Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F_0 , and others).
- Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

2. *Supplement — Changes Being Effected*

- a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess.
- b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For drug products and protein drug substances, changes to equipment of the same design and operating principle and/or changes in scale, except as otherwise provided for in this guidance (e.g., section VII.C.1.c).

2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.
3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved products.
4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified- release dosage form.
5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).
6. Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (506A(c)(2)(A)).

Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container and closure systems and in-process materials. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. An example of a test, analytical procedure, and acceptance criteria is: assay, a specific fully described high pressure liquid chromatography (HPLC) procedure, and 98.0-102.0 percent. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.¹⁸

A *regulatory* analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the U.S.

¹⁸ See FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

Pharmacopeia/National Formulary (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items.

The applicant may include in its application *alternative* analytical procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used.

In sections B-D below, the use of the term *analytical procedure* without a qualifier such as *regulatory* or *alternative* refers to analytical procedures used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Relaxing an acceptance criterion, except as otherwise provided for in this guidance (e.g., section VIII.C.1.b).
2. Deleting any part of a specification, except as otherwise provided for in this guidance (e.g., section VIII.D.2).
3. Establishing a new regulatory analytical procedure.
4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.
5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) one that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) one that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

6. Relating to testing of raw materials for viruses or adventitious agents:¹⁹ (1) relaxing an acceptance criteria, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes in specifications that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

I. Supplement — Changes Being Effected in 30 Days

- a. Any change in a regulatory analytical procedure other than editorial or those identified as major changes.
- b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate), except as provided for in section VIII.B.6.
- c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as provided for in section VIII.B.6.
- d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and

¹⁹ In this context, testing for adventitious agents is not considered to include tests that are found in an official compendium (e.g., USP <61>).

aseptic filling.

2. *Supplement — Changes Being Effected*

- a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.
- b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

D. Minor Changes (Annual Report)

The following are examples of changes in specifications that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Any change in a specification made to comply with an official compendium.
2. For drug substance and drug product, the addition, deletion or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.
3. Tightening of acceptance criteria.
4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

IX. PACKAGE

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for use with an ophthalmic ointment.
2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change to an ink and/or adhesive used on the permeable or semipermeable packaging component to one that has never been used in a CDER-approved product of the same dosage form, same route of administration, *and* same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).
3. A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

4. For sterile products, any other change that may affect product sterility assurance such as:²⁰
 - A change from a glass ampule to a glass vial with an elastomeric closure.
 - A change to a flexible container system (bag) from another container system.
 - A change to a prefilled syringe dosage form from another container system.
 - A change from a single unit dose container to a multiple dose container system.
 - Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
 - Changes in the size and/or shape of a container for a sterile drug product.
5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases).
6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. *Supplement — Changes Being Effected in 30 Days*
 - a. A change to or in a container closure system, except as otherwise provided for in this guidance.
 - b. Changes in the size or shape of a container for a sterile drug substance.

²⁰ Some of these identified changes, depending on the circumstances, may have to be filed as new NDAs or ANDAs instead of as supplements. Applicants can consult the appropriate CDER chemistry division/office if there are questions.

2. *Supplement — Changes Being Effected*

- a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2 regarding solid dosage forms).
- b. A change in or addition or deletion of a desiccant.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

- 1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.
- 2. A change in the size and/or shape of a container containing the same number of dose units, for a nonsterile solid dosage form.
- 3. The following changes in the container closure system of solid oral dosage form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products:²¹
 - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
 - Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).
 - Changes in packaging materials used to control odor (e.g., charcoal packets).
 - Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).

²¹ For sections IX.D.3 to 6, changes in the container closure system that result in product contact with a component material that has never been used in any CDER-approved product of the same type should be filed as a supplement — changes being effected in 30 days (IX.C.1) or prior approval supplement (IX.B.1).

- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).
- A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form products.
- A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the product.

4. The following changes in the container closure system of nonsterile liquid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical products):

- Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).

5. A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository).

6. The following changes in the container closure system of nonsterile semisolid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:

- Changes in the closure or cap.
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal.

- A change in the crimp sealant.

7. A change in the flip seal cap color, as long as the cap color is consistent with any established color coding system for that class of drug products.

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations. All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a prior approval supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.
5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another product.
7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement — Changes Being Effected)

A changes being effected supplement should be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) is specifically requested by FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.
2. Addition of a precaution arising out of a postmarketing study.
3. Clarification of the administration statement to ensure proper administration of the product.
4. Labeling changes, normally classified as major changes, that FDA specifically requests be implemented using a changes being effected supplement.

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201), without a change in the content of the labeling.
2. Editorial changes, such as adding a distributor's name.
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.
4. Labeling changes made to comply with an official compendium.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or to a reference listed drug (506A(c)(2)(B)).
2. Addition of a stability protocol or comparability protocol.
3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).
4. An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol.

B. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. *Supplement — Changes Being Effected in 30 Days*
 - a. Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be filed in a supplement — changes being effected in 30 days even if it is based on data obtained under a protocol approved in the application.
2. *Supplement — Changes Being Effected*

No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. An extension of an expiration dating period based on full shelf life data on full production batches obtained under a protocol approved in the application.
2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.
3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances.
4. Non-USP reference standards:
 - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
 - Tightening of acceptance criteria for existing reference standards to provide greater assurance of product purity and potency.

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes.

ATTACHMENT A
MANUFACTURING SITES

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (21 CFR 207.20). An *establishment* means a place of business under one management at one general physical location (21 CFR 207.3(a)(7)). A *general physical location* is reasonably construed to include separate buildings within the same city *if* the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and all inspected at the same time (ORA Field Management Directive No. 132).

For the purposes of determining the reporting category for moves between buildings, the terms *different manufacturing site* and *same manufacturing site* mean:

Domestic Establishments

Same manufacturing site:

- The new and old building are included under the same drug establishment registration number²²

and

- The same FDA district office is responsible for inspecting the operations in both the new and old building.

Different manufacturing site:

- The new and old building have different drug establishment registration numbers

or

- Different FDA district offices are responsible for inspecting operations in the new and old building.

For domestic establishments, the terms *same* and *different manufacturing site* supersede the terms *contiguous campus*, *same campus*, and *different campus* as used in the SUPAC guidances.

²² The registration number is the number assigned to the establishment by the district (ORA Field Management Directive No. 92). Currently, the registration number is the seven digit central file number (CFN).

Foreign Establishments

Foreign establishments are not currently required to register with the FDA. On May 14, 1999 FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until the time registration of foreign establishments is required, same and different manufacturing sites mean:

Same manufacturing site:

- A contiguous or unbroken site or a set of buildings in adjacent city blocks.

Different manufacturing site:

- New and old building not on a contiguous site or not in adjacent city blocks.

ATTACHMENT B
TYPE OF OPERATION AND CGMP INSPECTIONS

Section VI states that a change to a different manufacturing site should be filed in a prior approval supplement when (1) the new manufacturing site has never been inspected by FDA for the type of operation being moved, (2) the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or (3) the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

A *profile class system* is used by FDA to assist in (1) managing the CGMP inspection process, (2) evaluating the findings and the compliance follow-up needed, and (3) communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g., sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below). However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

The term *type of operation* refers to the specialized or even unique conditions and practices which are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process. These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all products at a given manufacturing site. Both the general and the specific conditions and practices are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and products may be produced at a manufacturing site or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a *profile class code*.

Generally, a satisfactory CGMP rating for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control. The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce in-process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation. If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site producing a terminally sterilized small volume parenteral product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Certain inspections may be required by program priorities even if a profile class code indicates an acceptable CGMP status. The current profile codes/classes for human drugs are:

ADM	Aerosol dispensed medication	NEC	Not elsewhere classified (when using this class, specific products are noted)
CBI	Biotechnology crude drug	OIN	Ointment, nonsterile (includes cream, jelly, paste)
CEX	Plant/animal extraction crude drug	POW	Powders (includes oral and topical)
CFS	Sterile bulk by fermentation crude drug	RAD	Radiopharmaceutical
CFN	Nonsterile bulk by fermentation crude drug	RSP	Radiation sterilization process
CHG	Capsule, prompt release	SNI	Sterile noninjectable
CRU	Crude bulk drugs-nonsynthesized	SOP	Soap
CSG	Capsules, soft gelatin	SSP	Steam sterilization process
CSN	Nonsterile bulk by chemical synthesis	SUP	Suppositories
CSP	Chemical sterilization process	SVL	Small volume parenterals (lyophilized)
CSS	Sterile bulk by chemical synthesis	SVS	Sterile-filled small volume parenterals
CTL	Control testing laboratories	SVT	Terminally sterilized small volume parenteral
CTR	Capsules, modified-release	TCM	Tablets, prompt-release
GAS	Medical gas (includes liquid oxygen and other)	TCT	Tablets, delayed-release
GSP	Gas sterilization process	TDP	Transdermal patches
HSP	Dry heat sterilization process	TSP	Fractional (tyndallization) sterilization process
LIQ	Liquid (includes solutions, suspension, elixirs, and tinctures)	TTR	Tablets, extended-release
LVP	Large volume parenterals	WSP	Water sterilization process

CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.)

Examples of postapproval manufacturing site changes and filing consequences:

- An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be filed in a prior approval supplement because the new manufacturing site doesn't have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out their packaging operations for immediate-release tablets (TCM) and capsules (CHG), and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet products should be filed in a prior approval supplement. The packaging site change for the capsule products should be filed as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate their product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form/type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form products, is considered to apply to all dosage forms, including those not actually produced at the site.

**ATTACHMENT C
CDER-APPROVED**

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. For example, certain changes in the container closure systems of solid oral dosage form products may be included in the annual report, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products (see section IX.D.3). If the primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage form products, then submission of the change in an annual report is not recommended.

CDER-approved products are considered those subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, *Inactive Ingredient Guide*, 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, the applicant has the option of filing the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, filing similar subsequent changes for other NDAs and ANDAs using the lower recommended reporting category.

GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other criteria for the tests described.

Active Ingredient/Drug Substance: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3).

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

Drug Product: A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

Final Intermediate: The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Inactive Ingredients: Any intended component of the drug product other than an active ingredient.

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical).

Intermediate: A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance.

Package: The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

Packaging Component: Any single part of a container closure system.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Reference Listed Drug: The listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3).

Satisfactory Current Good Manufacturing Practice (CGMP) Inspection: A satisfactory CGMP inspection is an FDA inspection during which (1) no objectionable conditions or practices were found during (No Action Indicated (NAI)) or (2) objectionable conditions were found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing and should follow the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at <http://www.fda.gov/opacom/backgrounder/foihand.html>.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specifications: The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials.

Validate the Effects of the Change: To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

EXHIBIT D



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

DEC 24 1996

TO ALL ANDA AND AADA APPLICANTS

Dear Sir or Madam:

As part of the ongoing initiatives to reinvent government, the Office of Generic Drugs (OGD), like most other Federal programs, is faced with reduced resources. In addition to diminishing resources, OGD experienced a significant increase in submissions in late 1995. This higher level of submissions has continued in 1996. These combined factors resulted in an increased backlog of pending submissions. In order to help minimize the impact of these factors on review times, OGD began a series of internal meetings to identify procedures that would help streamline the review process. In addition, OGD believes these efforts will improve communications with industry and reduce the overall time to approval of abbreviated applications.

This letter describes the first streamlining initiatives that affect the chemistry, bioequivalence and labeling review processes. OGD looks forward to implementing additional streamlining initiatives in the future. The letter also contains an update on a variety of application related matters that will be of interest to applicants.

The Office trusts the information will be useful to you. Your cooperation in these matters will assist us in our effort to improve the efficiency of the generic drug review process.

Sincerely yours,

D. L. Sporn

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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For ease in referencing the material contained in the letter, topics are presented in the following order at the specified pages:

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REVIEW ISSUES

COMMUNICATING NOT APPROVABLE DETERMINATIONS

Effective January 1, 1997, the Office of Generic Drugs (OGD) will provide most application related "not approvable" deficiencies, both major and minor, to ANDA/ANDAA holders via facsimile for unapproved original applications. This is expected to decrease time to final action on applications. However, for the present time, the Division of Bioequivalence will continue to issue deficiency letters as it has always done.

The facsimile will include the usual components of a deficiency letter, but not in the traditional letter format. It will include;

- A. A list of chemistry, manufacturing, and controls (CMC) deficiencies followed by additional CMC comments regarding status of methods validation, pre-approval inspection, and other related points.
- B. A list of labeling deficiencies.
- C. A list of microbiology deficiencies, if applicable.

A cover sheet will accompany the deficiency list which will provide instructions on how to respond to the facsimile.

To assist the Office in providing the facsimiles, applicants are requested to provide or update the facsimile number for its Regulatory Affairs contact person.

MAJOR NOT APPROVABLE DEFICIENCY PROCEDURES

Major CMC deficiencies identified by OGD will be sent to the applicant by facsimile. Responses from the applicant to these deficiencies will be regarded as a major amendment and should be submitted as an archival (hard) copy to OGD. OGD will not accept facsimile responses for major deficiencies.

MINOR NOT APPROVABLE DEFICIENCY PROCEDURES

For CMC deficiencies defined as minor, OGD will also communicate to the applicant by facsimile. The facsimile cover sheet that OGD sends to an applicant will identify the deficiency response as either a "Facsimile Amendment" or a "Minor Amendment". Procedures for responding to these two

types of amendments are as follows:

A. Facsimile Amendment

There will be some minor deficiencies for which OGD believes a complete response can be provided by the applicant within 30 days. These deficiencies will be provided by facsimile and will NOT stop the regulatory review clock.

The applicant will be asked to respond directly to OGD's document room by facsimile, followed with a hard copy. Facsimile amendments will be reviewed ahead of other priority or routine submissions pending in the reviewer's queue.

Should the complete response (facsimile and hard copy) not be received within 30 days, the applicant's response will be considered a minor amendment and placed into the reviewer's minor amendment queue.

B. Minor Amendment

There will be some minor amendments for which a response cannot be provided within 30 days. These will typically be for situations when the response is beyond the control of the applicant, e.g., Drug Master File (DMF) deficiencies. OGD will provide these deficiencies by facsimile and will STOP the regulatory review clock. In addition, the applicant's response (minor amendment) should be submitted as an archival(hard) copy to OGD and will be placed into the reviewer's queue according to OGD's first-in, first-reviewed policy. OGD will not accept facsimile responses for these minor amendments.

In order to evaluate the expected benefits of this new process, the Office will be monitoring the impact on action times. However, reports of industry experiences with this process are encouraged.

PHONE CONSULTATION FOLLOWING SECOND REVIEW CYCLE WITH MAJOR DEFICIENCIES

Applicants who find that an application continues to have major CMC deficiencies after the second review cycle are encouraged to call the appropriate Project Manager (PM) in OGD to discuss or clarify the deficiencies. Where appropriate the

PM will involve the chemistry reviewer and/or others in the discussion. The goal is to answer questions, assist the applicant to understand the identified deficiencies and, hopefully, eliminate further major deficiency reviews. In some cases meetings may be necessary to clarify these deficiencies. OGD will contact the applicant within approximately 30 days after issuance of the second major deficiency letter if the Office has not been contacted by the applicant. OGD will also use the same approach for subsequent reviews where major deficiencies remain.

Currently, OGD is unable to provide this level of service after the first review cycle due to the volume of such submissions and the Office's limited resources.

ALTERNATE DRUG SUBSTANCE FOR ORIGINAL APPLICATIONS

The Office of Generic Drugs has announced a change in policy regarding adding an alternate source of the new drug substance (NDS) to an original application prior to approval.

Previously, if an abbreviated application was otherwise approvable with the exception of an unsatisfactory inspection of Current Good Manufacturing Practices (cGMP) for the primary NDS supplier used to manufacture the exhibit/bioequivalence batch, it would not be approved until those cGMP issues were resolved. In order to qualify an acceptable alternate source of the NDS, a new exhibit batch based on the alternate source would be needed. Additionally, a bioequivalence study would be required (depending on dosage form) to support use of the alternate source.

For unapproved applications, OGD now allows substitution of an alternate source of the new drug substance based on assurance that the specifications and test data are essentially the same as those of the original source used in the exhibit batch (and bioequivalence study, if required) that would have been acceptable except for cGMP issues, etc. Additionally, the DMF must be found acceptable. Generally, a new *in vivo* bioequivalence study will not be required for the alternate exhibit batch, but it will be necessary to provide comparative dissolution data depending on the dosage form of the proposed product. This new policy is identical to the existing policy regarding post approval changes to provide for alternate sources of the NDS.

Note that there are some situations where this new policy would not apply and a new acceptable exhibit batch, an *in vivo* bioequivalence study, and comparative dissolution data would be required. This might be the case when there are significant differences in particle size or physicochemical

characteristics.

BIOEQUIVALENCE ISSUES

ELECTRONIC SUBMISSION PROJECT

Effective January 1, 1997, the Office of Generic Drugs will implement its program for electronic submission of bioequivalence data. The program was developed under contract with the University of Maryland (UM). Under the program, applicants that choose to, may prepare electronic submissions on diskette with the aid of a user-friendly program call Entry and Validation Program (EVA). EVA is free of charge to applicants through the UM's World Wide Web site (<http://mundes.ifsm.unbc.edu/~fdacom>). The Web site also permits applicants to register as participants and to obtain updated information on the program including any new versions of EVA. Companies can also ask technical questions through the Web site, which will be addressed by UM staff.

The program is expected to have a very positive impact on the efficiency of reviews, ultimately reducing review times. In addition, it is hoped the program will help reduce the time required to reach approval. Therefore, OGD strongly encourages firms to participate.

For most companies, the time to start planning the electronic submission is before study data are prepared. For those using Contract Research Organizations (CROs) to conduct bioequivalence studies, applicants could specify in their requirements that the CROs prepare the data in the requested format. CROs are encouraged to access the UM Web site and to become familiar with EVA and submission requirements. Applicants may also make electronic submissions for applications already submitted to the Office, but should contact the Bioequivalence Project Manager (Ms. Lizzie Sanchez, 301-594-7290) first, to make certain the electronic submission will be received in time for the review.

We hope to conduct training for applicants in conjunction with UM. Those applicants interested in such training are encouraged to register their interest through the UM Web site. Technical questions about the program may be addressed to the UM at 410-455-3888 or through the UM Web site. Regulatory questions may be addressed to the Bioequivalence Project Manager.

The electronic submission program is part of a larger strategy for Electronic Regulatory Submission and Review (ERSR) which will soon include the chemistry, manufacturing, and controls (CMC) portion of generic drug applications.

AVAILABILITY OF BIOEQUIVALENCE PROTOCOL REVIEWS

Firms frequently submit proposed *in vivo* bioequivalence study protocols to OGD. Often these are duplicative of already submitted and reviewed protocols. In order to decrease the burden of reviewing several protocols for the same drug product, OGD is now making available copies of acceptable protocols and related review comments. OGD believes that by utilizing completed review comments, firms will need to submit fewer protocols, freeing time for evaluation of applications. Copies may be obtained from the Drug Information Branch, HRP-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD, 20857. The current phone number for the Drug Information Branch is (301) 827-4573. Please note that this number was recently changed because that branch re-located.

The list of protocols available may be accessed through "FAX on Demand" at (800) 342-2722 or (301) 827-0577. You are encouraged to obtain an updated list by this means. However, the Division of Bioequivalence will also maintain a listing.

There are caveats to be borne in mind regarding this new resource:

- A. The material available will be redacted protocols and letters transmitting the review comments.
- B. It will take some time to prepare protocols and reviews for distribution through this process. Therefore, the number of different product protocols and review will gradually increase, over time.
- C. The procedure is new and may require fine tuning. Thus, comments and suggestions are encouraged. These may be submitted to Ms. Lizzie Sanchez at (301) 594-2290.
- C. There will be a transition period during which firms with pending requests for protocol review may be contacted regarding the imminent availability of a review of another protocol regarding the product for which they had submitted a protocol. The firm may wish to withdraw its protocol and use information available from the previously acceptable review.

Please note that though this service is available, the Division may be contacted should there appear to be circumstances necessitating review of another protocol for the

same drug product.

UPDATE ON ALBUTEROL INHALATION AEROSOL GUIDANCE

On January 27, 1994, OGD issued the guidance titled "Interim Guidance for Documentation of in vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)." Since its publication, the Office has had the opportunity to review additional information on various aspects of in vivo and in vitro testing conducted as described in the guidance and has concluded that a revision of the guidance is needed. A CDER working group developed recommendations for revision and presented them to a joint session of the Advisory Committee for Pharmaceutical Science (ACPS) (re-configuration of the Generic Drugs Advisory Committee - GDAC) and the Pulmonary Drugs Advisory Committee in August of 1996.

Therefore, should studies for albuterol metered dose inhalers (MDI's) be under consideration, sponsors are strongly encouraged to wait for the revised guidance, or, in the interim, discuss their planned study with the Division of Bioequivalence. The guidance will be developed as expeditiously as possible and the industry will be informed of its availability.

BIOEQUIVALENCE STUDIES TO BE CONDUCTED IN APPROPRIATE SUBJECTS

Though it is preferable to conduct bioequivalence testing in normal healthy volunteers, there are certain products for which use in healthy persons might be an unacceptable risk.

A. Cytotoxic drugs

Certain conditions and considerations regarding bioequivalence studies of cytotoxic drugs need to be specified. Please note the following:

21 CFR 320.31(a)(3) requires that any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an investigational new drug application (IND). An IND provides assurance that studies proposed will have adequate safeguards for the safety of the subjects.

It is therefore recommended that studies with the following products be conducted in the appropriate patient population. Note also that the listing (developed in conjunction with the Division of Oncologic Drug Products) is subject to updating and revision. Consultation with the Office is recommended if any questions arise.

Bisulfan	Chlorambucil
Cyclophosphamide	Etoposide
Hexamethylmelamine	Lomustine
Melphalan	Pipobroman
Procarbazine	Thioguanine
Uracil Mustard	Methoxsalen
Extramustine Phosphate	

2. Ipratropium

In order to fully evaluate the bioequivalence of this product, studies should be conducted in the appropriate patient population.

IN VIVO STUDIES UNDER SUPAC-IR

Under the Center's Guidance for Industry: Immediate Release Solid Oral Dosage Forms (SUPAC-IR), there are two types of post-approval changes for which *in vivo* bioequivalence testing is requested: Level 3 changes in components and composition as well as Level 3 manufacturing process changes. For generic drugs, the *in vivo* bioequivalence test should always compare the product after a post-approval change against the reference listed drug. However, in instances when a bioequivalence study is not necessary, dissolution studies should compare the applicant's generic product after a post-approval change against the same product prior to the change.

If there are any questions in regard to a reference product, please contact the Division of Bioequivalence for advice.

LABELING REVIEW CHANGES

The abbreviated application regulations require that side-by-side labeling comparisons be included with the submission of the original, unapproved application, with all differences between the proposed ANDA/ABDA and the reference listed drug (RLD) labeling annotated and fully explained [See 21 CFR 314.94(a)(8)]. Side-by-side comparisons enable reviewers to readily identify differences between the ANDA/ABDA and the reference listed drug labeling and/or the previous version of the applicant's labels and labeling.

ODG is now requesting a side-by-side comparison for all labeling changes submitted, not only in original applications, but also for all amendments and supplements. This comparison will help reduce the time required to review each new version of proposed labeling.

Additional actions to streamline the labeling review process have resulted in the following changes:

- A. OGD will provide pen and ink comments directly on a applicant's proposed labeling and attach those comments to the Not Approvable facsimile. This will eliminate the time consuming task of identifying where in the labeling changes should be made and explaining the needed changes in letter format. This will conserve reviewer's time, thus making more efficient use of OGD resources.
- B. Effective immediately, when changes are needed in labeling because of changes in the RLD labeling, OGD will either identify the specific changes to be made or will provide a copy of the most recently approved labeling of the RLD. In the past when MAJOR changes were required in the labeling, the applicant was required to obtain a copy of the cited approved labeling from the Freedom of Information (FOI) staff, then submit a supplement or amendment. This process added 4 to 5 weeks to the process of updating the ANDA/AADA labeling.

Please note that OGD will NOT supply labeling of the RLD BEFORE an application is filed. The most recent APPROVED labeling should be obtained from the FOI staff prior to preparation and submission of the labeling in an ANDA/AADA.

The Division of Labeling and Program Support highly recommends that ANDA/AADA applicants NOT utilize the Physician's Desk Reference (PDR) as the source for the most recently approved labeling of the innovator's product. Although the PDR may represent labeling that is available in the marketplace, some of this labeling may have been submitted to the Agency as a "Special Supplement - Changes Being Effected" (SSCBE). As such, it would have been implemented prior to FDA approval in accordance with 21 CFR 314.70(c). The FDA must still review, possibly recommend changes and approve the labeling before it is acceptable for use as model labeling for an ANDA/AADA product. In addition, other changes may have been made in the approved labeling after the publication of the PDR.

APPLICATION PROCESS ISSUES

Refusal to File Issues

The Office evaluates abbreviated applications for completeness and acceptability prior to filing them for review. OGD has identified many issues which previously would have resulted in refuse to file determinations which can be easily resolved by applicants. These are now communicated by OGD by telephone

rather than issuing a letter which can take weeks. Such items include:

No cGMP statement
FDA Form 356h does not contain an original signature
Improper patent certification
Exclusivity rights not addressed
No debarment/list of convictions statement
No certification of field copy
Need for additional copies of labeling

Applicants are given 10 working days to respond. If a response is not received in that time, a refuse to file letter is issued.

This approach has resulted in a decrease in refuse to file determinations and moves applications into the review queue more rapidly. Even with this approach, the refuse to file rate for applications remains high. Therefore, an update of the key reasons the Office refuses to file abbreviated applications follows:

A. DMF Issues

No authorization for the Drug Master File (DMF) or incomplete information about the DMF.

The DMF authorization must be from the DMF holder or its U.S. agent to permit the agency to refer to the DMF on behalf of the applicant. If the authorization is from the agent, an additional letter of appointment of the agent must also be included from the holder of the DMF (link to DMF holder). The authorization for the agency to refer to the DMF must reference the specific applicant, not another corporate entity related to the applicant.

For further information please refer to the CDER Guideline for Drug Master Files.

B. Inactive Ingredient Issues

Inadequate information on the characterization of inactive ingredients.

The regulations related to parenteral, ophthalmic, otic and topical dosage forms [21 CFR 314.94(a)(9)] state that applicants shall identify and characterize the inactive ingredients in the proposed drug product and provide information

demonstrating that the inactive ingredients do not affect the safety of the proposed drug product. Additionally, OGD's Interim Inactive Ingredients Policy dated November 17, 1994, address inactive ingredient issues in more detail. The Interim Inactive Ingredient Policy is available in the OGD Docket (No. 9050308).

Thus, applicants should demonstrate that the proposed drug product is qualitatively and quantitatively the same as the reference listed drug product for parenteral, ophthalmic, otic, and topical dosage forms. An applicant may seek approval of a drug product that differs from the RLD, in certain instances, as described in the regulations.

Generally, products for oral inhalation are considered topical products. Therefore, applicants for these products are requested to provide a qualitative and quantitative comparison. Please refer to the Interim Inactive Ingredient Policy for further guidance.

For other topical products, i.e., creams, lotions, gels, suspensions, and solutions an applicant is requested to provide the following information:

1. Qualitative Statement

A list of ingredients (test drug and reference drug) to show a qualitative comparison.

2. Quantitative Statement

The quantitative composition of the test drug and the results of analysis of the reference drug. It may not be possible to accurately analyze some inactive ingredients contained in the reference product. However, applicants should make their best efforts to quantitatively analyze the ingredients in the reference drug and submit the results in the application. If an ingredient cannot be analyzed, or if results are irrelevant or inconclusive, an explanation should be provided. Sponsors may use the Center for Drug Evaluation and Research Inactive Ingredient Guide (IIC) as a reference for safe maximum levels. If the ingredient levels are not listed, the sponsor may also refer to

other sources of information, such as other approved topical products where quantitative levels are known, recognized literature references or information from the ingredient manufacturer.

OGD does not require a quantitative or qualitative analysis beyond the normal analytical capabilities within the industry.

If applicants have questions regarding inactive ingredients, they may submit a request for the opinion of the OGD on the acceptability of inactive ingredients prior to the submission of an application. The Office can provide certain information in response to such requests.

C. Exclusivity Issues

Exclusivity right(s) or patent(s) not addressed.

Patents and exclusivity must be addressed. When there is no exclusivity or patent listed in the Orange Book, the applicant should provide a statement to this effect. It is also suggested that applicants verify they are using a current edition of the Orange Book and/or cumulative supplement as the basis for this information.

D. Packaging Information

No record of or incomplete packaging information on the exhibit batch.

This packaging information is requested in order for the application to be filed. This request is outlined in OGD's Policy and Procedure Guide #41-93.

ACCEPTANCE OF ANDA BASED ON A PENDING PETITION FOR A DETERMINATION OF REASONS FOR VOLUNTARY WITHDRAWAL OF THE REFERENCE LISTED DRUG

OGD can accept an Abbreviated New Drug Application that refers to a listed drug that has been voluntarily withdrawn from sales as long as the applicant provides evidence that a Citizen's Petition has been submitted to request a determination of whether a listed drug has been voluntarily withdrawn for safety or efficacy reasons. A Center response to that petition is not required for filing purposes. However, the Center must have made its determination on

relisting prior to the approval of the ANDA. (See 21 CFR 314.161 and 314.122)

DOCUMENTATION OF APPROPRIATE AUTHORIZATION OF AGENTS

It is acknowledged that there are many circumstances that require applicants to have other parties interact with the OGD on their behalf relative to specific applications. Frequently, written authorization for these agents is not contained in an application when submitted. The Office wishes to be cooperative in its response to applicant needs but must assure submitted material remains confidential and is not released or discussed with unauthorized individuals.

In order to allow for prompt responses, it is requested that written authorization be submitted to the application when filed or well before contact by an authorized agent is expected. Examples of who requires such authorization include:

- A. The U.S. agent of a foreign firm.
- B. A consultant to the firm that is expected to interact directly with OGD.
- C. Legal counsel to the firm on issues that may necessitate direct interaction with OGD.

INFORMATION FOR INSPECTIONS

United States agents for foreign establishments are very helpful to the Office of Compliance in assigning foreign inspections. It is, therefore, important that complete information (name, address, phone/fax numbers) of the U.S. agent be included in an application.

Central File Numbers (CFN) as identifiers for facilities are also of value in the scheduling of inspections. Please provide these numbers for all facilities included in the application. CFN's are obtained by applying for them through the FDA District Offices.

OTHER

WITHDRAWAL OF APPLICATIONS

The Office requests that firms make periodic internal assessments and withdraw pending applications they may not wish to pursue to approval. This action will allow conservation of OGD's information tracking and document control resources.

EXHIBIT E

No. 06-1249

In the Supreme Court of the United States

WYETH, PETITIONER

v.

DIANA LEVINE

*ON PETITION FOR A WRIT OF CERTIORARI
TO THE SUPREME COURT OF VERMONT*

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

DANIEL MERON <i>General Counsel</i>	PAUL D. CLEMENT <i>Solicitor General</i> <i>Counsel of Record</i>
GERALD F. MASOUDI <i>Associate General Counsel</i>	JEFFREY S. BUCHOLTZ <i>Acting Assistant Attorney</i> <i>General</i>
WENDY S. VICENTE <i>Attorney</i> <i>Department of Health and</i> <i>Human Services</i> <i>Washington, D.C. 20201</i>	EDWIN S. KNEEDLER <i>Deputy Solicitor General</i>
	DARYL JOSEFFER <i>Assistant to the Solicitor</i> <i>General</i>
	DOUGLAS N. LETTER PETER R. MAIER <i>Attorneys</i>
	<i>Department of Justice</i> <i>Washington, D.C. 20530-0001</i> <i>(202) 514-2217</i>

QUESTION PRESENTED

Whether state-law tort claims are preempted to the extent that they would impose liability for a drug manufacturer's use of labeling that the Food and Drug Administration approved after being informed of the relevant risk.

(I)

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61 Fed. Reg. 44,413 (1996)	10
63 Fed. Reg. (1998):	
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In the Supreme Court of the United States

No. 06-1249

WYETH, PETITIONER

v.

DIANA LEVINE

*ON PETITION FOR A WRIT OF CERTIORARI
TO THE SUPREME COURT OF VERMONT*

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is filed in response to the Court's order inviting the Solicitor General to express the views of the [REDACTED]. In the view of the United States, the petition for a writ of certiorari should be held pending this Court's decisions in *Riegel v. Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert Co., LLC v. Kent*, cert. granted, No. 06-1498 (Sept. 25, 2007), and then disposed of as appropriate in light of the decisions in those cases.

STATEMENT

1. Under the Federal Food, Drug, and Cosmetic Act (FDCA or Act), 21 U.S.C. 301 *et seq.*, a drug manufacturer may not market a new drug unless it has submitted a new drug application to the Food and Drug Administration (FDA) and received the agency's approval. 21 U.S.C. 355(a). An application must contain, among other things, "the labeling proposed to be used for such drug,"

(1)

21 U.S.C. 355(b)(1)(F) (Supp. V 2005); see 21 C.F.R. 314.50(c)(2)(i) and (e)(2)(ii); “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is * * * effective in use,” 21 U.S.C. 355(b)(1)(A) (Supp. V 2005); and “a discussion of why the benefits exceed the risks [of the drug] under the conditions stated in the labeling,” 21 C.F.R. 314.50(d)(5)(viii); see 21 C.F.R. 314.50(c)(2)(ix).

The FDCA also requires that drugs not be misbranded. 21 U.S.C. 331(a) and (b). A drug is misbranded if, among other things, the drug’s “labeling is false or misleading in any particular;” the labeling does not provide “adequate directions for use” or certain “adequate warnings;” the drug “is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof;” or the labeling does not comply with certain FDA regulations. 21 U.S.C. 352(a), (f) and (j). FDA has established specific requirements for prescription drug labeling. 21 C.F.R. Pt. 201.

FDA will approve a new drug application if it finds, among other things, that (i) the drug is “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof,” (ii) there is “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof,” and (iii) the proposed labeling is not “false or misleading in any particular.” 21 U.S.C. 355(d).

After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with use of the drug in humans, 21 C.F.R. 314.80, and must periodically submit

any new information that may affect FDA's previous conclusions about the safety, effectiveness, or labeling of the drug, 21 C.F.R. 314.81. See 21 U.S.C. 355(k) (post-approval reporting and record-keeping requirements); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901 *et seq.*, 121 Stat. 922 (enhancing FDA's authority to require postmarket studies and surveillance). FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e).

Following FDA's approval of an application, the manufacturer generally may not make changes to the drug, including "[c]hanges in labeling," without first submitting a supplemental application to FDA and securing the agency's prior approval for the change. 21 C.F.R. 314.70(b)(2)(v)(A). A manufacturer must submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. 201.57(c)(6). "An applicant may ask FDA to expedite its review of a supplement for public health reasons." 21 C.F.R. 314.70(b)(4). In addition, a manufacturer may change a drug's labeling at the same time that it submits a supplemental application to FDA, without waiting for the agency's approval of the change, if, among other things, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C). FDA interprets that regulation to permit changes without prior approval only to address "newly discovered risks." 47 Fed. Reg. 46,623 (1982). If a manufacturer makes a change before receiving FDA's approval, the agency may later reject the

change and order the manufacturer to cease distribution of the changed product. 21 C.F.R. 314.70(c)(7).

2. After FDA approved petitioner's new drug application for the anti-nausea drug Phenergan, petitioner informed FDA of adverse events in which Phenergan apparently was inadvertently injected intra-arterially, resulting in gangrene and amputation. See, e.g., Pet. App. 139a-140a (1967 report). Over the ensuing years, FDA and petitioner engaged in back-and-forth communications concerning the appropriate labeling to address the risks presented by inadvertent intra-arterial injection. See, e.g., *id.* at 141a-166a. As part of its deliberations, FDA convened an expert advisory committee to consider that question. *Id.* at 144a, 147a-148a.

As of 2000 (when the events giving rise to this suit occurred), the FDA-approved labeling stated, in part, that “[u]nder no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of subsequent gangrene.” Pet. App. 167a. The labeling went on to explain that the “preferred” method of administering the drug is “by deep intramuscular injection,” because intravenous administration can result, in some circumstances, in inadvertent intra-arterial injection. *Ibid.* For circumstances in which the drug is injected intravenously, the labeling described in detail how such injection should be done, in order “to avoid * * * inadvertent intra-arterial injection.” *Ibid.*

3. In April 2000, respondent sought treatment at a health center for headache and nausea. Pet App. 2a. The health center’s staff first administered Phenergan to respondent by intra-muscular injection. *Ibid.* When respondent’s nausea continued, the staff administered a second dose of Phenergan by intravenous injection into

her arm. *Ibid.* The intravenous injection was made by a procedure the parties refer to as IV push, whereby the Phenergan solution was not dripped through a free-flowing bag, but instead was directly injected into respondent's arm. See *id.* at 2a, 52a. The IV push apparently resulted in inadvertent arterial injection, which damaged respondent's arteries, caused gangrene, and required amputation of her hand and forearm. *Id.* at 2a.

Respondent brought and settled an action against the health center where she had received the injection of Phenergan. Pet. App. 50a. She also sued petitioner in a Vermont state court, asserting negligence and failure-to-warn claims premised on alleged inadequacies in the drug's labeling. *Id.* at 8a. Respondent asserted that "the label should not have allowed IV push as a means of administration, as it was safer to use other available options, such as intramuscular injection or administration through the tubing of a hanging IV bag." *Ibid.* After the trial court rejected petitioner's preemption defense, *id.* at 49a-74a, the jury found in respondent's favor, and the trial court entered judgment in the amount of \$6,774,000, *id.* at 3a.

4. a. The Vermont Supreme Court affirmed. Pet. App. 1a-34a. It interpreted 21 C.F.R. 314.70(c) to "allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." *Id.* at 13a. In the court's view, Section 314.70(c) was crucial to the preemption analysis: "While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, [Section] 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law" by making unilateral changes to FDA-approved labeling. *Id.* at 11a.

The Vermont Supreme Court also relied on a provision in the 1962 amendments to the FDCA that states that “[n]othing in th[ose] amendments * * * shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law.” Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 793. The court construed that provision to limit preemption to circumstances in which it would be physically impossible for a manufacturer to comply with both federal and state law. Pet. App. 21a. Here, the court determined, there was no such impossibility because there was no indication that FDA would have rejected a supplemental application seeking to strengthen the warning under Section 314.70(c). *Id.* at 17a.

b. Chief Judge Reiber dissented. Pet. App. 35a-48a. He explained that respondent’s state-law claims conflict with federal law because, while “FDA concluded that the drug—with its approved methods of administration and as labeled—was both safe and effective,” the “jury concluded that the same drug—with its approved methods of administration and as labeled—was ‘unreasonably dangerous.’” *Id.* at 35a (quoting *Town of Bridport v. Sterling Clark Lurton Corp.*, 693 A.2d 701, 704 (Vt. 1997)). Supporting that conclusion, in the Chief Judge’s view, is the fact that FDA does not merely establish minimum safety standards, but instead “balances its assessment of a drug’s safety against concerns for the drug’s efficacy, taking into account that a safer but less effective drug is not necessarily best for the public health overall.” *Id.* at 47a. With respect to drug labels, the Chief Judge explained, “FDA considers not only what information to include, but also what to exclude,”

in part because overwarning can do more harm than good. *Ibid.*

The Chief Judge also took issue with the majority's understanding of Section 314.70(c). Pet. App. 39a-41a. He explained that the regulation "allow[s] manufacturers to address newly discovered risks," but "does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." *Id.* at 40a.

DISCUSSION

Petitioners' claim [REDACTED] FDCA because the [REDACTED] Pet. App. [REDACTED]

[REDACTED] additional or different way [REDACTED]. The Vermont Supreme Court's contrary conclusion rests on its mistaken view that an FDA regulation, 21 C.F.R. 314.70(c), "allow[s] unilateral changes to drug labels whenever the manufacturer believes [the changes] will make the product safer." Pet. App. 13a. That interpretation of the regulation is wrong, because Section 314.70(c) permits unilateral changes based only on newly available information, not based on information that was previously available to FDA, such as the risk at issue here.

While the Vermont Supreme Court's decision is wrong, it does not warrant plenary review at this time. The decision below does not squarely conflict with any decision of a federal court of appeals or another state supreme court. Moreover, this Court's decisions in two pending FDA preemption cases—*Riegel v. Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert, LLC v. Kent*, cert. granted, No. 06-1498 (Sept.

25, 2007)—may shed significant light on the question presented in this case. Accordingly, the Court should hold the petition in this case pending its decisions in *Riegel* and *Warner-Lambert*, and then dispose of the petition as appropriate in light of its disposition of those cases.

A. Respondent's Claims Are Impliedly Preempted

Federal law preempts state laws that conflict with federal law, including state laws that either “make it ‘impossible’ for private parties to comply with both state and federal law,” *Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000), or that “stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,” *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). Because respondent’s claims challenge labeling that FDA [REDACTED] approval of the labeling therefor are preempted.

1. FDA’s approval of a drug, including its labeling, generally preempts state law claims challenging the drug’s safety, efficacy, or labeling
 - a. FDA may approve a new drug application only if it determines, among other things, that (i) the drug is “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof,” (ii) there is “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof,” and (iii) the proposed labeling is not “false or misleading in any particular.” 21 U.S.C. 355(d). Thus, FDA specifically considers and approves a drug’s labeling. Indeed, the agency’s consideration of safety and effectiveness is di-

rectly tied to its consideration of “the proposed labeling,” *ibid.*, in part because a drug’s safety and effectiveness depend on the conditions under which it is used (*e.g.*, its dosage, its method of administration, and its intended use). Labeling is “[t]he centerpiece of risk management,” as it “communicates to health care practitioners the agency’s formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively.” 71 Fed. Reg. 3934 (2006).

FDA’s review of a new drug application is similar to its premarket approval process for Class III medical devices, see 60 Fed. Reg. 39,180 (1995), which this Court has correctly described as “rigorous,” *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 477 (1996). As part of the approval process, an applicant must submit “the labeling proposed to be used for such drug,” 21 U.S.C. 355(b)(1)(F) (Supp. V 2005), as well as extensive information about the composition, manufacture, and specification of the drug, any studies of the drug’s pharmacological actions and toxicological effects in animals, any studies of the drug’s bioavailability and pharmacokinetics in humans, any clinical investigations of the drug, and “any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source.” 21 C.F.R. 314.50(d); see 21 U.S.C. 355(b)(1)(A) (Supp. V 2005).

If FDA is not ultimately satisfied that a drug is safe for use under the conditions of its labeling and that there is substantial evidence that the drug is effective when used according to the labeling, FDA cannot approve the application. 21 U.S.C. 355(d). Thus, FDA’s approval reflects its expert determination, based on a careful review of extensive scientific and technical infor-

mation, that a drug is safe and effective when used according to its labeling, and that the labeling satisfies federal requirements.

the Vermont Supreme Court thought. See Pet. App. 19a. Instead, FDA weighs health benefits against health risks. See 71 Fed. Reg. at 3934; 60 Fed. Reg. at 39,180. As this Court has explained, FDA "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use." *United States v. Rutherford*, 442 U.S. 544, 555 (1979); accord *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000). FDA has, for example, approved cancer treatments that are highly toxic and thus not "safe" as that term is ordinarily used, but that are nonetheless safe in the relevant sense under the FDCA because the potential benefits to health outweigh the risks. 61 Fed. Reg. 44,413 (1996); see *Brown & Williamson*, 529 U.S. at 142.

As explained above, a drug's safety and effectiveness are not determined in the abstract, divorced from its labeling. See 71 Fed. Reg. at 3934. Rather, FDA requires each new drug application to contain "a discussion of why the benefits exceed the risks [of the drug] *under the conditions stated in the labeling.*" 21 C.F.R. 314.50(d)(5)(viii) (emphasis added); see 21 C.F.R. 314.50(c)(2)(ix). If FDA then concludes that a drug's benefits outweigh its risks only under certain conditions, the agency may require appropriate labeling to reflect that determination. See, e.g., 21 C.F.R. 314.110(a).

Fed. Reg. at 3935. "Exaggeration of risk could discourage appropriate use of a beneficial drug," and thereby harm the public health. *Ibid.* In addition, excessive warnings can cause more meaningful risk information to "lose its significance." 44 Fed. Reg. 37,447 (1979); accord 71 Fed. Reg. at 3935; 65 Fed. Reg. 81,083 (2000). "Warnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Brooks v. Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir. 2001), cert. denied, 535 U.S. 1056 (2002). Thus, as the dissent explained, there are "a number of sound reasons why the FDA may prefer to limit warnings on product labels." Pet. App. 47a (quoting *Brooks*, 273 F.3d at 796).

For those reasons

That conflict is especially clear in this case because, as the dissent explained, any recovery under state law would be predicated on a finding that Phenergan, as labeled, was “unreasonably dangerous.” Pet. App. 35a (quoting *Town of Bridport v. Sterling Clark Lurton Corp.*, 693 A.2d at 704). That finding would directly conflict with FDA’s determination that the drug, as labeled, was safe and effective. *Id.* at 35a-36a. As such, respondent’s claims are preempted. See, e.g., *Geier*, 529 U.S. at 881-883 (holding that state suit seeking to impose

liability for failure to use a particular type of restraint system would stand as an obstacle to the federal agency's decision to encourage the use of a range of restraint systems); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001) (holding that state-law fraud-on-FDA claim was impliedly preempted because it would interfere with FDA's ability to strike a "somewhat delicate balance of statutory objectives").

2. Federal law precluded petitioner from unilaterally changing the FDA-approved labeling

The Vermont Supreme Court erroneously interpreted 21 C.F.R. 314.70(c) to "allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a. As discussed above, however, the FDCA requires a manufacturer to receive FDA's approval for a new drug's labeling. 21 U.S.C. 355(a) and (d). [REDACTED]

[REDACTED] See 21 C.F.R. 314.70. Here, for example, FDA instructed petitioner that the "final printed labeling * * * must be identical" to the approved labeling. Pet. App. 105. If manufacturers were free to change their labels without FDA approval, [REDACTED]

[REDACTED] The Vermont Supreme Court's view that "FDA approval of a drug label" is nothing more than "a first step," *id.* at 15a, is there-

fore fundamentally inconsistent with the federal regulatory framework.

Consistent with the stringent statutory and regulatory requirements for approval of a new drug in the first place, [REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] g. 21 C.F.R. 314.70(a)(2)(v). As a general rule, the manufacturer must obtain prior approval by FDA before making such changes. Section 314.70(c) provides a limited exception to that rule permitting “the holder of an approved [new drug application] to commence distribution of the [changed] drug product involved upon receipt by the agency of a supplement for the change” if, among other things, the change “add[s] or strengthen[s]” a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C).

As FDA explained when it proposed that regulation in 1982, however, [REDACTED]
[REDACTED]

[REDACTED] 47 Fed. Reg. at 46,623 (emphasis added). FDA explained that, “[a]lthough most changes in labeling would require the applicant to submit a supplement and obtain FDA approval before making a change,” some changes that “would make available *important new information* about the safe use of a drug product” could be made upon submission of a supplemental application. *Id.* at 46,635 (emphasis added); compare FDA, *Draft Guidance for Industry and FDA Staff, Modifications to Devices Subject to Premarket Approval (PMA)* 19 (Mar. 9, 2007) <<http://www.fda.gov/cdrh/ode/guidance/1584.pdf>> (explaining that a manufacturer may make unilateral changes to a device subject to FDA’s premarket approval only if “the

manufacturer has newly acquired safety-related information” that “was not previously considered by the FDA”).

Thus,

[REDACTED] which FDA can approve or reject, and must be based on material new information—not information that was previously available to FDA, nor even cumulative new information that does not add materially to the information that was previously available to the agency. As the dissent explained, S[REDACTED]

[REDACTED]
[REDACTED] different conclusions regarding the risk of accidental intra-arterial injection. Pet. App. 40a.
FDA’s interpretation of its own regulation is entitled to significant deference. See *Auer v. Robbins*, 519 U.S. 452, 461 (1997).

In this case, it does not appear that respondent relies on any material new information that was not available to FDA. The parties dispute whether FDA specifically and expressly rejected the stronger warning that respondent asserts should have been included in the labeling. See, e.g., Br. in Opp. 15-17. There is and can be no dispute, however, that FDA was presented with extensive information about the dangers of accidental intra-arterial injection from intravenous administration of the drug, and that Phenergan’s FDA-approved labeling provided specific guidance on how to inject the drug, either intramuscularly or intravenously, so as to reduce that risk. See p. 4, *supra*. Nor did the Vermont Supreme Court point to any marked change in the number or type of reported cases of accidental intra-arterial injection from intravenous administration that might have suggested that the risk was of a magnitude that was not

previously known at the time that FDA approved labeling that addressed that risk. Under a correct reading of Section 314.7, [REDACTED]

[REDACTED] labeling without prior FDA approval, and [REDACTED]

Moreover, even when a manufacturer makes a change at the same time that it submits a [REDACTED] application to FDA, [REDACTED]

[REDACTED] basis for a change." 21 C.F.R. 314.70(c)(3). The agency may then reject the change based on its own balancing of the relevant health risks and benefits. See 21 C.F.R. 314.70(c)(7). If FDA rejects the change, it may order the manufacturer to cease further distribution of the changed product. *Ibid.* Changed labeling also "remains subject to enforcement action" if FDA finds that the change "makes the labeling false or misleading." 71 Fed. Reg. at 3934; see 21 U.S.C. 352 (2000 & Supp. V 2005). Thus, [REDACTED]

[REDACTED] 1. Reg. at 3934. For these reasons, in practice manufacturers typically consult with FDA before making labeling changes that the manufacturer believes could appropriately be made unilaterally under 21 C.F.R. 314.70(c) while a supplemental application was pending before FDA. See 71 Fed. Reg. at 3934.

3. The 1962 amendments to the FDCA did not displace ordinary conflict-preemption principles

The Vermont Supreme Court mistakenly thought that Section 202 of the 1962 amendments to the FDCA precludes the application of ordinary conflict preemption principles in this case. See Pet. App. 21a-23a. That provision states as follows:

Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law.

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962).

At the outset, it is not clear to what extent Section 202 applies here. It is limited to "the amendments made by" the 1962 legislation. § 202, 76 Stat. 793. While those amendments broadened the scope of FDA's new drug approval process by requiring the agency to consider the efficacy as well as the safety of a drug, see § 102(b), 76 Stat. 781, FDA's new drug approval process predated the amendments, see 21 U.S.C. 355(a) and (d) (1958). Indeed, FDA approved Phenergan before 1962. See Pet. 6; Br. in Opp. 23 n.8.

Even assuming *arguendo* that Section 202 is relevant in this case, however, that provision means only that Congress did not intend the 1962 amendments to preempt the *field* of drug regulation; it does not manifest an intent to displace ordinary principles of *conflict* preemption. 71 Fed. Reg. at 3935 n.8. Indeed, Section 202 expressly contemplates preemption in circumstances involving "a direct and positive conflict." § 202, 76 Stat. 793.

The Vermont Supreme Court read that phrase to refer only to situations in which it would be impossible to comply with both federal and state law, as distinguished from situations in which state law would frustrate the purpose of the federal scheme. Pet. App. 21a-23a. That interpretation is incorrect. Before 1962, this Court had long used the phrase "direct and positive con-

flict" to refer to conflict preemption generally, not to a mere subset of such preemption. See, e.g., *United Constr. Workers v. Laburnum Constr. Corp.*, 347 U.S. 656, 663 n.5 (1954); *Sinnot v. Davenport*, 63 U.S. 227, 243 (1859). In so doing, the Court contrasted "direct and positive" conflict preemption to "field" preemption, not to some subset of conflict preemption. E.g., *Kelly v. Washington ex rel. Foss Co.*, 302 U.S. 1, 9-10 (1937). More generally, this Court has never "driven a legal wedge—only a terminological one—between 'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law." *Geier*, 529 U.S. at 873.

In any event, "[t]he Court has * * * refused to read general 'saving' provisions to tolerate actual conflict both in cases involving impossibility and in 'frustration-of-purpose' cases." *Geier*, 529 U.S. at 873-874 (citation omitted). That would appear to apply, *a fortiori*, to a provision that addresses only the effect of particular amendments, not the overall permanent code. See p. 16, *supra*. Moreover, even when a statute contained a savings clause providing that "[c]ompliance with" a federal safety standard "does not exempt any person from *any* liability under common law," 15 U.S.C. 1397(k) (1988) (emphasis added), this Court held that the savings clause did not preclude the application of ordinary conflict preemption principles, including frustration of purpose principles. *Geier*, 529 U.S. at 868, 873-874. The savings clause here, which expressly provides for conflict preemption, likewise does not displace ordinary conflict preemption principles.

[REDACTED] concerning [REDACTED]
[REDACTED] the labeling of drugs. FDA complained that the govern-

[REDACTED] [REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]

ment's "current view[] is that "FDA approval of labeling under the [FD&C] Act does not preempt or contrary State law," especially considering that "FDA interprets the [FD&C] Act to octain a labeling 'ceiling' for labeling." 71 Fed. Reg. at 3934, 3935. The agency also recognized[] that FDA's regulation of drug labeling will not preempt all State law actions." *Id.* at 3936. FDA then provided some specific examples of circumstances in which state laws are preempted, but it did not attempt to exhaust such circumstances. See *id.* at 3935-3936 (noting that "at least" those examples would be preempted). In this brief, the government has articulated a more generally applicable rule of decision, consistent with the framework and examples set forth in the preamble, that reflects FDA's explanation in that preamble that [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

s. See *id.* at 3934-3935.*

* While respondent argues (Br. in Opp. 8, 28) that FDA's 2006 preamble reflected a change in the agency's position, she relies solely on snippets from Federal Register notices that did not squarely address, much less discuss, the preemption question here. See 65 Fed. Reg. at 81,103 (stating that proposed *changes* to existing labeling rules would not have federalism implications); 63 Fed. Reg. 66,384 (1998) (response to comments concerning Medication Guides for "a small number of products," *id.* at 66,379); 44 Fed. Reg. at 37,437 (responding to comment that FDA should use different administrative procedures).

B. This Court Should Hold The Petition For A Writ Of Certiorari Pending The Decisions in *Riegel* and *Warner-Lambert*

Although the Vermont Supreme Court's decision is wrong, it does not warrant this Court's plenary review at this time.

1. Petitioner asserted (Reply 1) for the first time in its reply brief that the decision below conflicts with *Dowhal v. Smithkline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004). There is no conflict. In *Dowhal*, California law required over-the-counter stop-smoking products containing nicotine to provide a specific health warning. *Id.* at 3-4. When the drug companies asked FDA for permission to change their labels to comply with the California law, FDA repeatedly denied their requests, told them to continue to use a different FDA-approved warning, and stressed that “[a]ny additional or modified warning may render the product misbranded.” *Id.* at 5-6. FDA was concerned that a stronger warning against the use of stop-smoking products would harm the public health by causing pregnant women to continue smoking instead of using the (less harmful) stop-smoking products. *Id.* at 4-5. Even when FDA ultimately permitted the companies to modify their warning labels, it prohibited them from using the particular labels required by the California law. *Id.* at 10-11. Against that unusual backdrop, the California Supreme Court correctly held that the state law was preempted. *Id.* at 11.

There is no square conflict because the *Dowhal* court tied its holding, not to FDA's approval of a new drug application, but to the agency's subsequent, specific prohibition of the warnings that would have complied with

California law. 88 P.3d at 10-11. On the facts of this case, in contrast, the Vermont Supreme Court determined that “FDA has not indicated that a stronger warning would be misleading.” Pet. App. 13a; see *id.* at 16a-19a. While FDA had rejected alternative labeling proposed by petitioner, the court below determined that there was no indication that FDA did so “to preserve the use of IV push as a method of administering Phenergan.” *Id.* at 17a. Thus, the two decisions are reconcilable based on the differing findings of fact in each case, and the Vermont Supreme Court might have found preemption in a case like *Dowhal* even under its erroneous impossibility standard of conflict preemption. To be sure, petitioner may dispute the Vermont Supreme Court’s interpretation of the record in this case. And the United States submits [REDACTED] respondent’s claims are [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] But those disagreements with the decision below do not amount to a conflict in legal authority.

2. Petitioner also relies (Reply 1-2) on a circuit split concerning the preemptive effect of FDA’s premarket approval of Class III medical devices. That conflict is real, but is not directly implicated here because this case involves implied preemption based on FDA’s approval of a new drug application and regulations governing changes in labeling, not express preemption based on FDA’s premarket approval of a medical device. Cf. 21 U.S.C. 360k(a) (expressly preempting certain requirements with respect to medical devices). Most importantly, this Court already granted review in *Riegel* to determine the

preemptive scope of FDA's premarket approval of a Class III medical device, and the Court heard argument in that case on December 4, 2007.

As petitioner's reliance (Reply 1-2) on the medical-device cases reflects, [REDACTED]

[REDACTED] While the FDCA contains an express preemption provision concerning devices (but not drugs), see 21 U.S.C. 360k, this Court has determined that implied preemption principles are relevant to the interpretation of that provision. See *Lohr*, 518 U.S. at 500; *id.* at 508 (Breyer, J., concurring).

Moreover, FDA's review of new drug applications and its premarket approval process for Class III devices are similar. See 60 Fed. Reg. at 39,180-39,181. In both instances, FDA conducts an extensive review of a product's safety and efficacy, balances health benefits against health risks in determining whether to grant approval, and generally precludes the manufacturer from making changes without the agency's prior approval. See U.S. Br. at 10-14, *Riegel*, *supra* (No. 06-179); pp. 8-14, *supra*. Under each regulatory regime, the manufacturer can make unilateral changes in labeling only in narrow circumstances while its supplemental application is pending with FDA. See *ibid.* Accordingly, this Court's resolution of *Riegel* is likely to be instructive on the question presented here.

In addition, the petition in *Warner-Lambert* (which the Court granted after inviting the views of the Solicitor General in this case) poses the related question whether the FDCA impliedly preempts state tort claims that require a court to determine, as a condition for imposing damages liability, whether a drug manufacturer defrauded FDA in a new drug application and whether

FDA would have denied or withdrawn approval of the drug but for that fraud. See Pet. at (i), *Warner-Lambert, supra*. That case differs from this one because the question there involves preemption of state-law determinations of fraud on FDA, while the question here involves preemption of common-law tort claims based on FDA's approval of a new drug application. Nonetheless, because *Warner-Lambert* involves implied preemption of claims involving FDA's approval of a new drug application, the decision in *Warner-Lambert* may also shed light on the proper resolution of the question in this case. For that reason as well, the Court should hold the petition in this FDA preemption case pending its resolution of the two FDA preemption petitions it has already granted for this Term.

CONCLUSION

The Court should hold the petition for a writ of certiorari pending its disposition of *Riegel v. Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert Co., LLC v. Kent*, cert. granted, No. 06-1498 (Sept. 25, 2007), and then dispose of the petition as appropriate in light of its disposition of those cases.

Respectfully submitted.

DANIEL MERON <i>General Counsel</i>	PAUL D. CLEMENT <i>Solicitor General</i>
GERALD F. MASOUDI <i>Associate General Counsel</i>	JEFFREY S. BUCHOLTZ <i>Acting Assistant Attorney General</i>
WENDY S. VICENTE <i>Attorney</i> <i>Department of Health and Human Services</i>	EDWIN S. KNEEDLER <i>Deputy Solicitor General</i>
	DARYL JOSEFFER <i>Assistant to the Solicitor General</i>
	DOUGLAS N. LETTER
	PETER R. MAIER <i>Attorneys</i>

DECEMBER 2007

EXHIBIT F

No. 06-179

In the Supreme Court of the United States

DONNA S. RIEGEL, INDIVIDUALLY AND AS
ADMINISTRATOR OF THE ESTATE OF
CHARLES R. RIEGEL, PETITIONER

v.

MEDTRONIC, INC.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

BRIEF FOR THE UNITED STATES
AS AMICUS CURIAE SUPPORTING RESPONDENT

PAUL D. CLEMENT
Solicitor General
Counsel of Record

PETER D. KEISLER
Assistant Attorney General

EDWIN S. KNEEDLER
Deputy Solicitor General

DARYL JOSEFFER
*Assistant to the Solicitor
General*

DOUGLAS N. LETTER
SHARON SWINGLE
Attorneys

DANIEL MERON
General Counsel
Department of Health and
Human Services
Washington, D.C.

Department of Justice
Washington, D.C. 20530-0001
(202) 514-2217

QUESTION PRESENTED

Whether, under the express preemption provision in 21 U.S.C. 360k, the Food and Drug Administration's premarket approval of a medical device preempts state-law tort claims relating to the safety or efficacy of that device.

(I)

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BRIEF FOR THE UNITED STATES
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INTEREST OF THE UNITED STATES

This case presents the question whether the Food and Drug Administration's (FDA's) premarket approval of a medical device preempts state claims relating to the safety or efficacy of that device. FDA administers the premarket approval process for medical devices and monitors devices' safety after they are marketed. The decision in this case will affect that responsibility. At the Court's invitation, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. a. The Medical Device Amendments of 1976 (MDA), 21 U.S.C. 360c *et seq.*, to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 301 *et seq.*, sort medical devices into three classes. See 21 U.S.C. 360c(a)(1). Class I and II devices are subject to regulatory controls or standards, but do not require pre-

(1)

market approval. See 21 U.S.C. 360c(a)(1)(A) and (B); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 476-477 (1996).

A device falls within Class III if (i) it “presents a potential unreasonable risk of illness or injury,” or is purported to be used to sustain or support human life or to have substantial importance in preventing impairment of human health, and (ii) there is inadequate evidence for FDA to determine that controls or standards authorized for Class I or II devices would provide reasonable assurance of safety and effectiveness. 21 U.S.C. 360c(a)(1)(C). In general, a Class III device requires premarket approval (PMA) by FDA unless it was marketed for use before the MDA’s enactment or it is “substantially equivalent” to a device that is already lawfully on the market. 21 U.S.C. 360e(a) and (b)(1)(A) and (B), 360(k). Fewer than 1% of new devices require premarket approval. Pet. App. 13a.

FDA’s PMA process for the relatively few devices that require it is “rigorous.” *Lohr*, 518 U.S. at 477. A manufacturer must submit: full reports of all studies and investigations, including clinical investigations, of the device’s safety and effectiveness; a full statement of the components, ingredients, properties, and principles of operation of the device; a full description of the methods used in, and facilities and controls used for, the manufacture, processing, packing, and installation of the device; a reference to any performance standard that would apply if the device were a Class II device, and information showing that the device satisfies that standard or justifying any deviation from it; any sample of the device or its components requested by FDA; and the proposed labeling. See 21 U.S.C. 360e(c)(1); 21 C.F.R. 814.20. FDA may request additional information from the manufacturer, and may also consult with a scientific advisory committee made up of outside experts. See 21 C.F.R. 814.44, 814.20(b)(13). The agency conducts an in-depth review of requests for premarket approval, devoting an average of 1,200 hours to each application. See *Lohr*, 518 U.S. at 477.

FDA may grant premarket approval for a Class III device only if it finds, among other things, that (i) there is “reasonable assurance” of the device’s “safety and effectiveness” under the conditions of use included in the proposed labeling, and (ii) the proposed labeling is neither false nor misleading. 21 U.S.C. 360e(d)(1)(A), (2)(A), (B) and (D). In determining safety and effectiveness, FDA must “weigh[] any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.” 21 U.S.C. 360c(a)(2)(C). FDA may impose restrictions on the sale or distribution of the device as a condition of premarket approval, see 21 U.S.C. 360e(d)(1)(B)(ii); 21 C.F.R. 814.82(a)(1), and it may also impose device-specific restrictions by regulation, see 21 U.S.C. 360j(e)(1).

Following FDA’s premarket approval, a manufacturer must submit a supplemental application to FDA and receive its approval before making any changes to a device that affect its safety or effectiveness. See 21 U.S.C. 360e(d)(6)(A)(i); 21 C.F.R. 814.39(a). The same process that applies to an original PMA application generally applies to a supplemental application. See 21 U.S.C. 360e(d)(6)(B); 21 C.F.R. 814.39(c). With only narrow exceptions, the manufacturer also must receive FDA’s approval before making any changes to the labeling of a device. See 21 C.F.R. 814.39(a) and (d)(1).

Manufacturers are also required to collect and report to FDA information on certain adverse events related to the device after it has been approved. See 21 U.S.C. 360i(a); 21 C.F.R. Pt. 803. The manufacturer must report within 30 days any incident in which a device may have caused or contributed to a death or serious injury, or in which the device malfunctioned in a manner that would likely cause or contribute to serious injury if the malfunction recurred. See 21 C.F.R. 803.10(c)(1), 803.50(a)(1)-(2). The manufacturer must report such an incident within five days if remedial action is required “to prevent an unreasonable

risk of substantial harm to the public health." See 21 C.F.R. 803.10(c)(2)(i).

A device manufacturer is also required to provide annual reports to FDA. See 21 C.F.R. 803.55(b), 814.84. Among other things, an annual report must identify any reports in the scientific literature about the device, as well as any unpublished reports of data from clinical investigations or nonclinical laboratory studies involving the device about which the manufacturer knows or reasonably should know. See 21 C.F.R. 814.84(b)(2).

Based on new information reported to FDA or other information known to the agency, FDA may withdraw premarket approval of a Class III medical device if it finds, among other things, that the device no longer satisfies the standards for premarket approval. 21 U.S.C. 360e(e)(1).

b. The MDA's express preemption provision states:

[N]o State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement—

- (1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and
- (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.

21 U.S.C. 360k(a). FDA is authorized to exempt some state or local requirements from preemption. 21 U.S.C. 360k(b).

FDA's regulations implementing Section 360k provide that "State or local requirements are preempted only when [FDA] has established specific counterpart regulations or there are other specific requirements applicable to a particular device." 21 C.F.R. 808.1(d). The regulations further explain that state or local requirements potentially subject to preemption include those "having the force and effect of law (whether established by

statute, ordinance, regulation, or court decision).” 21 C.F.R. 808.1(b). Under the regulations, a general state prohibition against adulterated or misbranded devices may be preempted if it “has the effect of establishing a substantive requirement for a specific device, e.g., a specific labeling requirement,” that “is different from, or in addition to, a Federal requirement.” 21 C.F.R. 808.1(d)(6)(ii).

2. The Evergreen Balloon Catheter is a Class III medical device used to open clogged arteries. Pet. App. 3a. FDA granted premarket approval for the device in 1994, and approved respondent’s supplemental applications in 1995 and 1996. *Id.* at 3a-4a. Charles Riegel was injured after an Evergreen Balloon Catheter ruptured while he was undergoing angioplasty. *Id.* at 4a. The physician used the device in contraindicated circumstances, and overinflated the device contrary to warnings on its label. *Ibid.*

Charles Riegel and his wife Donna Riegel brought this suit against respondent, alleging negligent design, testing, inspection, manufacture, distribution, labeling, marketing, and sale of the catheter; strict liability; breach of express warranty; breach of implied warranty; and loss of consortium. Pet. App. 4a-5a. The district court held that all of petitioners’ claims except those for negligent manufacturing and breach of express warranty were preempted by Section 360k(a). See *id.* at 55a-74a. The court subsequently granted summary judgment to respondent on the merits of the non-preempted claims. *Id.* at 75a-91a.

3. The court of appeals affirmed. Pet. App. 1a-54a. In holding that the bulk of petitioners’ claims were preempted, the court construed the term “requirement” in Section 360k to encompass the design and labeling for the device set forth in an approved PMA application. *Id.* at 26a-28a. The court explained that FDA may impose conditions on premarket approval in order to ensure that a device is safe and effective, and that federal law requires a manufacturer to comply with the specifications set forth in an approved PMA application. *Id.* at 9a.

The court of appeals determined that the imposition of tort liability based on the allegedly defective character of a device or label would subject the manufacturer to state-law requirements “different from, or in addition to,” the federal requirements embodied in the approved PMA application. Pet. App. 32a, 35a-36a. In contrast, the court determined that petitioners’ negligent manufacturing claim is not preempted because it is premised on an alleged violation of federal requirements. *Id.* at 36a.

While characterizing the question as a “close” one, Judge Pooler would have held that none of petitioners’ claims are preempted. Pet. App. 43a, 50a-54a.

SUMMARY OF ARGUMENT

The court of appeals correctly held that petitioners’ claims are preempted to the extent that they seek to impose liability on respondent for not departing from an FDA-approved design or labeling requirement imposed in the premarket approval process. Section 360k generally preempts any state “requirement” that is “different from, or in addition to, any [federal] requirement” and that “relates to the safety or effectiveness of the device or to any other matter included in a [federal] requirement.” 21 U.S.C. 360k(a).

For a Class III device to obtain premarket approval, FDA must determine that there is reasonable assurance that the device is safe and effective and that its label is not false or misleading. FDA undertakes an exhaustive scientific review to determine whether those requirements are satisfied. In doing so, FDA does not merely police minimum standards of safety. Instead, FDA weighs potential health risks against benefits. If the agency grants approval, it does so for a specific design and label based on that weighing, and the manufacturer is then barred from changing the FDA-approved design or label without FDA approval (subject only to limited exceptions that do not appear to apply here). Thus, the premarket approval process imposes federal requirements with preemptive effect under Section 360k.

The state-law claims in dispute here would impose requirements that are different from, or in addition to, those federal requirements. As five Justices concluded in *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996), state common-law damages actions impose “requirements” subject to preemption under Section 360k. The claims at issue here are premised on the assertion that the Evergreen Balloon Catheter, in the form and with the label approved by FDA, is not safe and effective. Thus, the common-law duties on which those claims are based would impose additional or different requirements. Moreover, subjecting a manufacturer to liability for not departing from an FDA-approved design or label would interfere with FDA’s ability to protect public health by balancing the risks and benefits of a particular design or label. For example, a state requirement that additional warnings must be included in the labeling for a device could dilute the effectiveness of more meaningful risk information, or deter beneficial uses of the device, contrary to FDA’s judgment that the existing label appropriately balances the health risks and benefits.

Finally, preemption is not limited to state requirements that apply *exclusively* to medical devices intended for human use, as petitioners contend. State requirements are preempted “with respect to a device intended for human use.” 21 U.S.C. 360k(a). That means that Section 360k(a) does not preempt the application of general state requirements to matters *other than* devices intended for human use; it does not mean that States can regulate such devices in any way they wish so long as they also regulate other things as well.

ARGUMENT**FDA'S PREMARKET APPROVAL OF A MEDICAL DEVICE
PREEMPTS STATE TORT CLAIMS CHALLENGING THE DE-
SIGN OR LABELING APPROVED BY FDA**

Congress expressly preempted, with respect to devices intended for human use, any state “requirement” that is “different from, or in addition to, any [federal] requirement” and that “relates to the safety or effectiveness of the device or to any other matter included in a [federal] requirement.” 21 U.S.C. 360k(a). That provision precludes state tort suits to the extent that they seek to impose liability on a device manufacturer for *not* departing from an FDA-approved design or label.

A. FDA's Premarket Approval Process Imposes Specific Federal Requirements

The court of appeals correctly held that FDA's premarket approval of a Class III device imposes specific federal requirements applicable to the device, and thus has preemptive effect. Pet. App. 25a-29a.

1. *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996), establishes the analytical framework for this case. In *Lohr*, this Court held that FDA's determination under 21 U.S.C. 360(k) that a device is substantially equivalent to a legally marketed device does not impose any federal “requirements” that preempt state law. See *Lohr*, 518 U.S. at 493. The Court explained that the manufacturer's contrary position in that case “exaggerate[d] the importance of the [substantial-equivalence] process,” in part because FDA had determined only whether the device was substantially equivalent to a legally marketed device, not (as here) whether it was safe or effective. *Id.* at 492-493. In doing so, the Court emphasized that FDA's substantial-equivalence determination “is by no means comparable to the PMA process.” *Id.* at 478-479.

This Court also held in *Lohr* that FDA's “general federal regulations governing the labeling and manufacture of all medi-

cal devices” do not preempt state tort claims. 518 U.S. at 497. The Court explained that, under FDA’s regulations concerning the preemptive scope of the MDA, “state requirements are preempted ‘only’ when the FDA has established ‘specific counterpart regulations or . . . other specific requirements applicable to a particular device.’” *Id.* at 498 (quoting 21 C.F.R. 808.1(d) (1995)). Those FDA preemption regulations are entitled to “substantial weight,” in part because Congress delegated to FDA the authority to grant exemptions from preemption—an authority that requires FDA to assess the preemptive effect of the MDA and the agency’s own actions on state laws. *Id.* at 496. Consistent with FDA’s preemption regulations, the Court determined that the *general* federal mandates on which the manufacturer relied in *Lohr* “reflect[ed] important but entirely generic concerns about device regulation generally, not the sort of concerns regarding a specific device or field of device regulation” that give rise to preemption. *Id.* at 501.

2. As this Court recognized in *Lohr*, a premarket approval is “by no means comparable” to a substantial-equivalence determination under Section 360(k). 518 U.S. at 478-479; see *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 348 (2001); Pet. App. 25a-27a. Unlike a substantial-equivalence determination, see *Lohr*, 518 U.S. at 493, FDA will grant premarket approval only if there is “reasonable assurance” that the device is safe and effective under the proposed conditions of use, and the proposed labeling is not “false or misleading in any particular,” 21 U.S.C. 360e(d)(1)(A), (2)(A), (B) and (D). As part of FDA’s “rigorous” review of those questions (*Lohr*, 518 U.S. at 477), an applicant is required to submit extensive information, including scientific studies that generally must be undertaken pursuant to FDA’s published standards. See 21 U.S.C. 360e(c)(1); 21 C.F.R. 814.20; p. 2, *supra*.

FDA encourages applicants to meet with it before submitting an application, so that FDA can “provide the applicant with the

agency's determination of the type of valid scientific evidence that will be necessary." FDA, *Device Advice—Premarket Approval* (Device Advice) (visited Oct. 19, 2007) <<http://www.fda.gov/cdrh/devadvice/pma/printer.html>>. After an application is filed, FDA may request any additional information needed to determine whether the device is safe and effective and properly labeled. See 21 U.S.C. 360e(d)(3)(A)(ii); 21 C.F.R. 814.37(b). FDA may also refer an application to a panel of experts, who provide FDA with a "report and recommendation respecting approval of the application, together with all underlying data and the reasons or basis for the recommendation." 21 U.S.C. 360e(c)(2); see 21 C.F.R. 814.44(a) and (b). "In general, all PMAs for the first-of-a-kind device are taken before the appropriate advisory panel for review and recommendation." Device Advice.

If the available information is ultimately insufficient to provide reasonable assurance of safety or effectiveness, FDA does not approve the application. 21 U.S.C. 360e(d)(2). Instead, FDA will informally determine whether a manufacturer will voluntarily provide additional information or make changes to a device's design or label that would permit approval. If those discussions are unsuccessful, FDA will either: (i) issue an "approvable letter" stating that the agency could approve the application if the applicant submitted specific additional information or agreed to conditions on approval, 21 C.F.R. 814.44(e); (ii) issue a "not approvable letter" describing the deficiencies in the application, 21 C.F.R. 814.44(f); or (iii) deny the application outright, 21 C.F.R. 814.45. FDA approves about 60% of PMA applications. See FDA, *Annual Report 41* (2004) <<http://www.fda.gov/cdrh/annual/fy2004/ode/2004.pdf>>. The other applicants typically receive approvable or not approvable letters. See *ibid.*

FDA devotes approximately 1,200 hours to a typical PMA review. See *Lohr*, 518 U.S. at 477. While this Court found that substantial-equivalence determinations "provide little protection to the public," *id.* at 493, premarket approvals reflect FDA's

expert judgment, rendered after exhaustive analysis, that there is reasonable assurance that the devices are in fact safe and effective and properly labeled.

3. FDA's premarket approval imposes "specific requirements applicable to a particular device." *Lohr*, 518 U.S. at 498 (quoting 21 C.F.R. 808.1(d) (1995)). The MDA requires that a device be safe and effective, and that its label not be false or misleading. 21 U.S.C. 360e(d). FDA's premarket approval gives specific content to those general requirements as applied to a particular device. The agency approves a specific design and label based on the agency's expert balancing of the health risks and benefits, and the MDA generally requires the manufacturer not to make subsequent changes without FDA's approval.

a. Contrary to petitioners' contention (Br. 24) that FDA reviews devices only for "minimum standards" of safety and effectiveness, the MDA directs FDA to "weigh[] any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," 21 U.S.C. 360c(a)(2)(C). Under that standard, FDA conducts a risk-benefit analysis to determine whether safety risks (whatever their magnitude) are warranted in light of the potential benefits. See, e.g., H.R. Rep. No. 853, 94th Cong., 2d Sess. 16-17 (1976); Device Advice. FDA's risk-benefit balancing for devices is parallel to the risk-benefit balancing it undertakes pursuant to 21 U.S.C. 355(d) as part of the pre-market approval process for drugs. See *United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("[T]he Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.").

Applying that approach, FDA has, for example, approved cancer treatments that are highly toxic and thus not "safe" as that term is ordinarily used, but that are nonetheless safe in the relevant sense under the FDCA because the potential benefits to health outweigh the risks. 61 Fed. Reg. 44,413 (1996); see *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000).

FDA has likewise approved a ventricular assist device for use in children with failing hearts, even though the survival rate for children with the device is under 50%. The agency explained that the device's benefits outweighed its significant risks. FDA, *Summary of Safety and Probable Benefit* 20 (2004) (Summary) <<http://www.fda.gov/cdrh/pdf3/H030003b.pdf>>.

In determining whether benefits outweigh risks, FDA may also consider the availability of other drugs, devices, or courses of treatment, as well as their safety profiles. As then-FDA Commissioner David Kessler testified in 1996, FDA "must determine if each new drug or device is safe enough in view of its anticipated benefits and the comparative benefit of other available treatments." *Testimony Before the Senate Comm. on Labor and Human Resources* <<http://www.hhs.gov/asl/testify/t960221a.html>>. Thus, when FDA approved the ventricular assist device discussed above, it relied in part on "the risks and benefits associated with alternative methods of treatment," which had high mortality rates. See Summary 20.

If similar, safer products are on the market, the agency requires a heightened health benefit to justify the heightened risk. For example, FDA determined in 2005 that Bextra should be withdrawn from the market because it presented greater safety risks than other drugs with comparable efficacy, and the manufacturer withdrew it. See FDA, *Alert for Healthcare Professionals* (2005) <<http://www.fda.gov/cder/drug/InfoSheets/HCP/valdecoxibHCP.pdf>>; *FDA Memorandum* 17 (2005) <<http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf>>.

FDA also weighs the overall health consequences of including particular warnings in the labeling. As FDA has explained, "[e]xaggeration of risk could discourage appropriate use of a beneficial drug." 71 Fed. Reg. 3935 (2006). The same is true for devices. Excessive warnings in the medical area risk deterring the use of critically important products. Thus, a warning label

must strike a balance between notifying users of potential dangers and not unnecessarily deterring beneficial uses. See *ibid.*

Moreover, the more warnings included in labeling, the less effective each constituent warning becomes. Warning of theoretical risks can cause more meaningful risk information to “lose its significance.” 44 Fed. Reg. 37,447 (1979); accord 71 Fed. Reg. at 3935; 65 Fed. Reg. 81,083 (2000). Indeed, “[o]verwarning has the effect of not warning at all. The reader stops paying attention to excess warnings.” FDA, *Write It Right* 7 (1993). Thus, there are “a number of sound reasons why the FDA may prefer to limit warnings on product labels.” *Brooks v. Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir. 2001), cert. denied, 535 U.S. 1056 (2002).

In *Lohr*, this Court emphasized that FDA had not “weighed the competing interests relevant to the particular requirement in question” or “reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases.” 518 U.S. at 501. Because FDA undertakes such a weighing as part of its premarket approval process, according preemptive effect to FDA’s premarket approvals is fully consistent with *Lohr*.

b. Once FDA granted premarket approval for the Evergreen Balloon Catheter based on the agency’s risk-benefit balancing, respondent could not have lawfully marketed a product that deviated from the approved version nor made any changes affecting the safety or efficacy of the device, including labeling changes, without first submitting a supplemental application to FDA. See 21 U.S.C. 360e(d)(6); 21 C.F.R. 814.39(a). The supplemental premarket approval process is similar to the initial PMA process. “All procedures and actions that apply to an [original application] * * * also apply to PMA supplements except that the information required in a supplement is limited to that needed to support the change.” 21 C.F.R. 814.39(c).

While petitioners argue (Br. 31) that applicants may make some changes without prior FDA approval, that is true only in

very limited circumstances that do not appear to apply here. Some changes in labeling, quality controls, or manufacturing processes may go into effect before FDA review if they “enhance[] the safety of the device.” 21 C.F.R. 814.39(d). As FDA recently explained in a draft guidance document, however, even those types of changes may be made without prior FDA approval only if “the manufacturer has newly acquired safety-related information” that “was not previously considered by the FDA.” FDA, *Draft Guidance for Industry and FDA Staff, Modifications to Devices Subject to Premarket Approval (PMA)* 19 (Mar. 9, 2007) (Draft Guidance) <<http://www.fda.gov/cdrh/ode/guidance/1584.pdf>>. Unilateral changes based on information available at the time of FDA’s approval could upset FDA’s balance of health risks and benefits, and thus “undermine” the PMA process. *Ibid.* Indeed, it would make little if any sense to permit unilateral changes immediately following FDA’s approval based on the same information that FDA had already considered.

Even if a manufacturer relies on new information to support a safety-enhancing change to a label, it still must obtain prior approval for any changes that affect both safety *and* efficacy. Draft Guidance 20. Though such a change would (in the manufacturer’s view) improve a device’s safety, it could also reduce health benefits, and thus affect the overall risk-benefit tradeoff. In this case, it appears that the exceptions to prior approval are beside the point, in part because petitioners’ tort claims do not appear to be based on newly available information. And, in any event, the statute and regulations vest in FDA, not States or juries, the authority to accept or reject the changes, whether or not the manufacturer has put them into effect in the meantime.

c. Petitioners argue (Br. 27) that, although FDA can impose design requirements with preemptive effect by regulation, the PMA process does not impose such requirements because FDA merely approves the applicant’s proposed design. That is incorrect. If FDA finds that a proposed device is not safe or effective,

it can condition its grant of premarket approval on the manufacturer's making specified changes to the device. 21 C.F.R. 814.44(e) and (f). In FDA's experience, manufacturers often agree to make such changes, even before FDA formally requires them as a condition of approval, in order to receive premarket approval. There is no meaningful basis for distinguishing between a specification imposed by regulation and the same specification imposed as a condition of premarket approval. In either case, a manufacturer could not deviate from the requirement without risking a violation of the MDA. Thus, FDA's regulations provide that federal "requirements" include not only "regulations," but also "other specific requirements applicable to a particular device." 21 C.F.R. 808.1(d).

Similarly, it makes no difference whether the approved device is identical to the one initially submitted by the applicant for approval, or was modified in the course of FDA's review. As the court of appeals explained, it would be perverse to subject respondent to greater potential tort liability on the ground that, because the device was safe and effective in the form submitted to FDA, it did not require changes or additional safeguards as a condition of premarket approval. Pet. App. 27a-28a. Whether or not the specifications were modified in the approval process, the applicant is generally barred from making changes without FDA's prior approval. Once the premarket approval process is complete, the manufacturer, with exceptions not relevant here, cannot lawfully market a product that deviates from the approved version. The specifications, as to both product and label, developed in the approval process become the requirements for lawfully marketing the device.

B. Petitioners' Tort Claims Would Impose State-Law Requirements

Just as the premarket approval process imposes requirements, petitioners' state-law claims would impose requirements on the design and labeling of the device.

1. Petitioners argue at length (Br. 14-23) that *no* state common-law duties are “requirements” subject to preemption. As the court of appeals explained, this Court has already rejected that contention. See Pet. App. 30a-32a.

While a four-Justice plurality of the *Lohr* Court predicted that “few, if any, common-law duties have been pre-empted by this statute,” 518 U.S. at 502, a majority of this Court disagreed. Writing for herself and three other Justices, Justice O’Connor “conclude[d] that state common-law damages actions do impose ‘requirements’ and are therefore pre-empted where such requirements would differ from those imposed by the [MDA].” *Id.* at 509. She explained that “state common-law damages actions operate to require manufacturers to comply with common-law duties.” *Id.* at 510. “The obligation to pay compensation can be, indeed is designed to be, a potent method of governing conduct and controlling policy.” *Ibid.* (quoting *San Diego Bldg. Trades Council v. Garmon*, 359 U.S. 236, 247 (1959)).

Writing separately, Justice Breyer “basically agree[d] with Justice O’Connor’s discussion of this point and with her conclusion.” 518 U.S. at 503. Justice Breyer explained that distinguishing between a state agency regulation requiring a particular design and a jury verdict imposing liability for failure to use that design would produce the “anomalous result” of “grant[ing] greater power (to set state standards ‘different from, or in addition to,’ federal standards) to a single state jury than to state officials acting through state administrative or legislative law-making processes.” *Id.* at 504. Thus, Justice Breyer concluded that, “ordinarily, insofar as the MDA pre-empts a state requirement embodied in a state statute, rule, regulation, or other administrative action, it would also pre-empt a similar requirement that takes the form of a standard of care or behavior imposed by a state-law tort action.” *Id.* at 504-505.

The Court reached the same conclusion in *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504 (1992), and *Bates v. Dow Agro-*

sciences LLC, 544 U.S. 431 (2005). *Cipollone* held that “[t]he phrase ‘[n]o requirement or prohibition’ sweeps broadly and suggests *no distinction* between positive enactments and common law; to the contrary, those words *easily encompass* obligations that take the form of common-law rules.” 505 U.S. at 521 (plurality opinion) (emphases added); accord *id.* at 548-549 (Scalia, J., concurring in the judgment in part and dissenting in part). In *Bates*, this Court again held that “requirements” “reaches beyond positive enactments, such as statutes and regulations, to embrace common-law duties.” 544 U.S. at 443.¹

Petitioners err in arguing (Br. 22) that “requirements” should be read to exclude common-law requirements because, at the time Congress enacted Section 360k, this Court had not yet construed a similar provision in any other statute to include common-law requirements. That rationale would have applied with equal force in *Cipollone*, because that was the first case in which this Court construed the term “requirement” in an express preemption clause. But the meaning of a statutory term stems from its ordinary usage and statutory context, not whether it has previously been construed by this Court. Cf. *Cipollone*, 505 U.S. at 521 (plurality opinion) (explaining that the term “requirements” “plainly” and “easily” includes common-law duties).

2. Petitioners argue (Br. 19-21) that the conclusion that common-law standards of care are “requirements” is inconsistent with the statutory structure. There is no inconsistency. Petitioners assert (Br. 13) that “requirements” cannot encompass state

¹ Petitioners rely (Br. 37) on *Bates*’ statement that “an event, such as a jury verdict, that merely motivates an optional decision is not a requirement.” 544 U.S. at 445. That passage does not address the question whether the substantive standard of care sought to be enforced in a common-law claim is a requirement (a question *Bates* answers in the affirmative, see *id.* at 443). Instead, it addresses the separate question whether requirements that do not directly apply to a product’s label or packaging are nonetheless requirements “for labeling or packaging,” as required by the statute at issue in *Bates*. See *id.* at 444-445. That question is not implicated here.

tort duties because Section 360k(b), which authorizes FDA to exempt from preemption a state or local “requirement” that satisfies certain conditions, “cannot workably be applied to damages claims.” But nothing in the statute bars FDA from granting an exemption for a requirement developed at common law. FDA may grant an exemption if either (i) a state requirement is more stringent than the corresponding federal requirement, or (ii) a state requirement is “required by compelling local conditions” and compliance with the requirement would not cause the device to violate a federal requirement. 21 U.S.C. 360k(b)(1).

While it may be more difficult for a common-law requirement to satisfy the conditions for an exemption, that does not mean that FDA lacks authority to grant an exemption if a common-law requirement satisfies either of the statutory prongs. Common-law judges are not unable to impose clear requirements. Some common law rules are very clear. See, e.g., *Ling v. Jan's Liquors*, 703 P.2d 731, 635 (Kan. 1985) (no liability at common law for furnishing liquor to intoxicated person). Common-law requirements can be clearly explained in opinions and are often clear enough for state legislators to replace a common-law requirement with one imposed by positive law. See, e.g., N.Y. Gen. Oblig. § 11-101 (imposing liability for furnishing liquor in some circumstances). In any event, while petitioners assume that Congress intended to ensure the availability of an exemption for every type of “requirement” subject to preemption, that assumption does not follow from the statutory text. Even if the conditions for granting an exemption meant that some types of requirements were not eligible for exemptions, that does not mean that those requirements would somehow lose their status as requirements.²

² FDA’s regulations do not expressly identify judicial or common-law rules as a subject for exemption, but do not rule them out, either. See 21 C.F.R. 808.20(e)(1) (State or locality must identify the “statute, rule, regulation, or ordinance” for which it seeks an exemption).

Petitioners also rely (Br. 20) on 21 U.S.C. 360h(d), which provides that an FDA order requiring public notice that a device poses an unreasonable risk of substantial harm does “not relieve a person from liability under Federal or State law,” including “damages for economic loss.” While that provision contemplates that *some* state-law actions are not preempted, it nowhere suggests that *no* such actions are preempted. Nor does it shed light on *which* such actions are preempted, which is the question here.

The more telling contextual evidence comes from the statute’s drafting history. The preemption provision in the bill initially passed by the Senate applied only to “a standard or regulation which prescribes any requirements as to” specified topics. S. Rep. No. 33, 94th Cong., 1st Sess. 72 (1975). By ultimately enacting the broader text of Section 360k(a)—which refers to “any requirement,” not only a requirement prescribed by a standard or regulation—Congress rejected a provision that was limited to state positive law in favor of one that is not. Moreover, as the House Report explained, Congress’s concern was that “if a substantial number of differing requirements applicable to a medical device are imposed by jurisdictions other than the Federal government, interstate commerce would be unduly burdened.” H.R. Rep. No. 853, *supra*, at 45. That concern does not turn on the form or source of a requirement.

C. The State-Law Requirements At Issue Here Are Different From, Or In Addition To, The Federal Requirements

The court of appeals correctly determined which of petitioners’ state-law claims assert duties that are different from or in addition to federal requirements, and are therefore preempted. See Pet. App. 32a, 35a-36a.

- 1. Common-law claims are preempted insofar as they assert that a device in its FDA-approved form is not safe or effective for use as directed in the FDA-approved labeling**

Petitioners' negligent-manufacturing claim is not preempted "to the extent it rest[s] on the allegation that the particular Evergreen Balloon catheter that was deployed during Mr. Riegel's angioplasty had not been manufactured in accordance with the PMA-approved standards." Pet. App. 35a. Such a claim would not impose an additional or different *requirement*; instead, it would provide a *remedy* for respondent's alleged failure to comply with a state law that parallels federal requirements. See 21 C.F.R. 808.1(d)(2); *Lohr*, 518 U.S. at 495; *id.* at 513 (O'Connor, J., concurring in part and dissenting in part).

In contrast, the other claims at issue here are premised on the assertion that the device, "in its present PMA-approved form, is in some way defective and therefore requires modification." Pet. App. 32a. Any judgment in petitioners' favor on those claims would necessarily rest on a finding that respondent was required, under state law, to alter the FDA-approved product specifications or labeling. As such, those state-law claims would impose requirements that are different from, or in addition to, the federal requirements.³

- 2. The claims at issue here would interfere with FDA's expert balancing of health risks and benefits**

The conclusion that the MDA preempts the claims at issue here is buttressed by the extent to which those claims would interfere with FDA's expert balancing of a device's health risks

³ Like petitioners' negligent-manufacture claim, their express-warranty claim is not preempted because it would merely provide a remedy for the violation of a state law that parallels a federal requirement. Pet. App. 72a. The district court entered summary judgment on the merits of that claim, however, and petitioners did not appeal that aspect of the judgment. *Id.* at 6a n.3.

and benefits. In *Lohr*, the Court looked to the statute's "overarching concern that pre-emption occur only where a particular state requirement threatens to interfere with a specific federal interest." 518 U.S. at 500. Justice Breyer likewise concluded that "[i]t makes sense, in the absence of any indication of a contrary congressional (or agency) intent, to read the pre-emption statute (and the pre-emption regulation) in light of * * * basic [conflict] pre-emption principles." *Id.* at 508.

a. Permitting a state jury to impose liability on the basis that a device FDA found to be safe and effective is *not* safe or effective would clearly interfere with the agency's ability to utilize the premarket approval process to balance the risks and benefits of Class III medical devices. The MDA is a "balanced" statute designed "to assure [both] that the public is protected from unsafe and ineffective medical devices" and "that innovations in medical technology are not stifled by unnecessary restrictions." H.R. Rep. No. 853, *supra*, at 12. In keeping with the latter concern, FDA balances a device's health risks against its benefits, and approves even devices that pose significant risks if their benefits outweigh the risks. See pp. 11-13, *supra*. Thus, premarket approval reflects FDA's expert determination that a device is on balance beneficial to human health, and therefore *should* be on the market. In such circumstances, a jury's imposition of liability based on a device's FDA-approved design or label would interfere with the balance struck by Congress in the MDA, and by FDA in approving the particular device.

Consider the example Justice Breyer used in *Lohr*. See 518 U.S. at 504. If FDA approves a hearing aid with a one-inch wire, a jury's imposition of liability on the theory that a two-inch wire should have been used would conflict with FDA's expert judgment. While petitioners assert (Br. 38) that the basis for a jury verdict is not always so clear, that hardly diminishes the concern. Imprecise standards can frustrate the federal regulatory balance as much as (if not more than) clear rules. What matters is not

the precision of the state law, but its conflict with federal policy. And in this example, the conflict is clear: FDA found that the device was safe and effective in a particular form, and the jury found that it was not.

Claims that challenge a device's FDA-approved label would similarly intrude upon FDA regulation. Over-warning poses serious health risks. See pp. 12-13, *supra*. As FDA has explained, "product liability and medical malpractice lawsuits, together with increasing litigation costs, ha[ve] caused manufacturers to become more cautious and include virtually all known adverse event information [in labels], regardless of its importance." 65 Fed. Reg. at 81,083. The consequence is "to limit physician appreciation of potentially far more significant" risks. 71 Fed. Reg. at 3935. The critical importance of providing appropriate warnings for medical devices—and, in particular, the most complex and highest-risk devices—further supports the conclusion that Congress intended FDA to use its expert judgment concerning the appropriate warnings for a particular medical device, and not to permit that judgment to be second guessed by lay juries.

b. Petitioners argue (Br. 40) that there is no conflict because "PMA does not preclude a later determination that the device is not safe and effective." Petitioners note in that regard (see Br. 40-41) that FDA has authority to change its mind and to withdraw its premarket approval of a device. That point only underscores, however, that Congress charged FDA, not state juries, with the responsibility to determine whether a device remains safe and effective and, thus, whether to withdraw the agency's approval.

Manufacturers must provide extensive information to FDA following approval of a medical device, including prompt reporting of adverse events that might be related to the device. See pp. 3-4, *supra*. FDA also conducts "routine postmarket inspections" of manufacturing facilities and other sites, and receives complaints from members of the public. FDA, *Ensuring the*

Safety of Marketed Medical Devices 11-13, 15 (2006) <<http://www.fda.gov/cdrh/postmarket/mdpi-report.pdf>>. Based on all of those sources of information, FDA may withdraw premarket approval for a variety of reasons, including that the agency no longer believes that the device satisfies the requirements for premarket approval. 21 U.S.C. 360e(e)(1). When FDA has not taken that action, however, its premarket approval of the device—and the federal requirements that result from that approval—remain in effect.⁴

d. FDA's conclusion that state tort liability would undermine its ability to balance risks and benefits is similar to the agency policy judgment to which this Court deferred in *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000). There, as here, the agency did not merely impose minimum safety standards. *Id.* at 874-875. Instead, it determined that public safety was best served by permitting manufacturers to install a variety of different passive restraint systems in their vehicles. *Id.* at 881. The Court held that a state suit seeking to impose liability for failure to use a particular type of restraint system would stand as an obstacle to the federal agency's decision. *Id.* at 881-883; see also, e.g., *Chicago & N.W. Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311, 325, 327 (1981). So too here, imposing liability on a manufacturer for using an FDA-approved design or altering an FDA-approved label would conflict with FDA's determination that the design and label appropriately balance the health risks and benefits.

FDA's understanding of its premarket approval process, and its judgment respecting the extent to which state law would interfere with that process, are entitled to deference. As this

⁴ That does not mean that injured persons are necessarily without a remedy. Petitioners' express-warranty and negligent-manufacturing claims were not preempted. See Pet. App. 70a-72a. In any event, FDA's decision to grant and not withdraw premarket approval strongly suggests that a device is not defective.

Court explained in *Lohr*, “Congress has given the FDA a unique role in determining the scope of § 360k’s pre-emptive effect.” 518 U.S. at 495-496. It is FDA that makes a case-specific determination regarding the safety and effectiveness of a device, and it is FDA’s approval of the design and labeling of the device that requires the manufacturer to adhere to those specifications in order to market the device. FDA’s role in administering the MDA makes it “uniquely qualified to determine whether a particular form of state law ‘stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.’” *Ibid.* (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)).

Petitioners argue (Br. 33-34) that FDA’s judgment respecting the conflict between premarket approval and state tort duties is not entitled to deference because FDA changed its view on the matter in 2004, and its position is not set forth in a formal regulation. As explained in the government’s petition-stage brief (at 16-17), however, the United States’ earlier position was based in part on proposed regulations that FDA has since withdrawn, and its prior position is inconsistent with FDA’s current understanding and application of the risk-management principles discussed above (*e.g.*, the need to prevent over-warning). Neither FDA’s reasoned change in position, nor the absence of a formal agency regulation addressing the specific question presented here, negates deference. See, *e.g.*, *Auer v. Robbins*, 519 U.S. 452, 461-462 (1997) (deferring to agency view set forth in amicus brief); *Motor Vehicle Mfrs. Ass’n v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 41-42 (1983) (holding that agency’s changed position is entitled to deference so long as the agency provides a reasoned explanation for the change).

3. The federal and state requirements at issue here are not equivalent

Petitioners argue (Br. 39) that their claims are not pre-empted because they are based on duties equivalent to federal statutory requirements for a Class III device, such as the prohi-

bition against misbranding and the requirement of reasonable assurance that a device is safe and effective when used in accordance with its labeling.

That claim was neither pressed nor passed upon in the court of appeals. Nor did petitioners raise it in their petition for a writ of certiorari. Thus, that claim is not properly before this Court. See, e.g., *Adickes v. S.H. Kress & Co.*, 398 U.S. 144, 147 n.2 (1970). Indeed, it would make little sense for this Court to undertake, in the first instance, to determine the elements of petitioners' state-law causes of action and to compare them to federal statutory and regulatory requirements. Cf. *Bates*, 544 U.S. at 447 (remanding for the court of appeals to undertake that task).⁵

In any event, petitioners' argument is wrong. In *Lohr*, this Court held that common-law claims that allege violations of FDA regulations are not preempted. 518 U.S. at 495. The court explained that "a damages *remedy* does not amount to the additional or different '*requirement*' that is necessary under the statute." *Ibid.* (emphases added). Significantly, however, the only requirements at issue there were FDA's "general" regulations applicable to "every medical device." *Id.* at 497-498.

Here, in contrast, the relevant federal "requirements" are not merely the general standards for premarket approval (such as safety and effectiveness). Instead, as discussed above, they include the specific design and labeling requirements imposed as part of the PMA process. A state-law finding of liability for not modifying the FDA-approved design or label would conflict with those specific requirements, because it would be based on a determination that an FDA-approved design was not safe or effective, or an FDA-approved label was inadequate.

Bates is inapposite for similar reasons. In that case, this Court construed the preemption provision of the Federal Insecti-

⁵ The United States' petition-stage brief (at 14-15) pointed out that petitioners had not preserved a claim that the state and federal requirements were equivalent. In their supplemental brief, petitioners did not dispute that point.

cide, Fungicide, and Rodenticide Act (FIFRA), which provides that a State “shall not impose or continue in effect any requirements for labeling or packaging in addition to or different from those required under this subchapter.” 7 U.S.C. 136v(b). This Court held that FIFRA would not preempt the plaintiffs’ state failure-to-warn claim if the elements of that claim were substantively equivalent to FIFRA’s prohibition on the sale of “misbranded” products. 544 U.S. at 447.

This case is fundamentally different from *Bates* because, under FIFRA, the Environmental Protection Agency (EPA) did not evaluate either the product’s efficacy or the accuracy of statements about efficacy in the proposed labeling. *Bates*, 544 U.S. at 440. Because EPA had never “passed on the accuracy of” the relevant statements in the product’s label, it had done nothing to “further refine [its] general [misbranding] standards in any way that [wa]s relevant to [the plaintiffs’] allegations” in *Bates*. *Id.* at 440, 453 n.27. Here, in contrast, FDA determined that there is reasonable assurance that the device is safe and effective in its current form, and that its labeling is accurate. Moreover, FIFRA, unlike the MDA, does not have a comprehensive goal of “uniformity,” but rather “authorizes a relatively decentralized scheme that preserves a broad role for state regulation.” *Id.* at 450.

D. Preemption Does Not Turn On Whether State Requirements Also Apply To Matters Other Than Medical Devices Intended For Human Use

Petitioners argue (Br. 34-36) that the common-law duties on which they rely are not preempted because they apply to matters other than medical devices intended for human use. That contention is incorrect.

1. Section 360k(a) provides that “no State or political subdivision of a State may establish or continue in effect *with respect to a device intended for human use* any requirement * * * which is different from, or in addition to, any requirement applicable under this chapter to the device” (emphasis added). Con-

trary to petitioners' assumption, the phrase "with respect to a device intended for human use" does not mean that only those requirements that apply *exclusively* to devices intended for human use are preempted. That phrase does not follow and modify the term "requirement." Instead, it follows and modifies the phrase "no State * * * may establish or continue in effect." Thus, it means that state requirements that apply both to devices intended for human use and to other matters are not preempted in their entirety, but instead are preempted only insofar as they apply "with respect to" devices intended for human use.

Petitioners' contrary reading is illogical. A state law's interference with federal requirements for devices intended for human use is in no way lessened by the state law's application to other matters. There is, for example, no reason that Congress would want to preempt a state statute that imposes design requirements on devices intended for human use, but to exempt altogether a state statute that imposes the same design requirements on devices intended for both human and animal use. In either case, Congress has an identical interest in preempting the statute with respect to medical devices intended for human use. The same is true of a common law duty that applies to, but is not limited to, medical devices intended for human use. Compare *Morales v. TWA*, 504 U.S. 374, 386 (1992).

FDA's regulations are consistent with that common-sense reading of the statutory text. They explain that the statute preempts state requirements "whether established by statute, ordinance, regulation, or court decision." 21 C.F.R. 808.1(b) (emphasis added). Petitioners rely (Br. 36) on a provision stating that the statute does not preempt "State or local requirements of general applicability where the purpose of the requirement relates either to other products in addition to devices (e.g., requirements such as general electrical codes, and the Uniform Commercial Code (warranty of fitness)), or to unfair trade practices in which the requirements are not limited to devices." 21 C.F.R.

808.1(d)(1). When FDA proposed that regulation, it explained that its intent was to exclude from preemption “requirements of general applicability that relate *only incidentally* to medical devices,” such as “general fire and electrical codes.” 42 Fed. Reg. 30,384 (1977) (emphasis added); see *ibid.* (same). Neither the regulatory text nor the preamble states that general tort duties of care fall outside the scope of preemption. Unlike fire codes or restrictions on unfair trade practices, such duties do not relate only incidentally to devices. Instead, they directly regulate every aspect of the device itself, including its very design.

The more relevant regulation is 21 C.F.R. 808.1(d)(6)(ii). Under that provision, “a State or local requirement prohibiting the manufacture of adulterated or misbranded devices” is “[g]enerally” not preempted, but is preempted when it “has the effect of establishing a substantive requirement for a specific device, e.g., a specific labeling requirement.” As discussed, petitioners’ tort claims would have precisely that effect because any imposition of liability would be based on a finding that the FDA-approved design or labeling is inadequate in some respect. Indeed, a jury verdict or common-law judge’s opinion can be understood as taking a general legal rule and applying it in a way that establishes a substantive requirement for the specific device at issue.

A contrary reading of the statute or regulations would effectively exempt all common-law claims (and many positive-law claims) from preemption. Petitioners have identified no general common-law duties that apply only to medical devices intended for human use, and the United States is aware of none. Petitioners’ position is thus difficult to square with the regulations’ determination that requirements “established by * * * court decision,” as well as general requirements that “ha[ve] the effect of establishing a substantive requirement for a specific device,” are preempted. 21 C.F.R. 808.1(b) and (d)(6)(ii). In any event, FDA’s interpretation of its regulations is entitled to deference. See, e.g., *Auer*, 519 U.S. at 461-462.

2. Nor can petitioners' position be reconciled with this Court's decision in *Lohr*. Providing the decisive fifth vote, Justice Breyer rejected the *Lohr* plurality's view that "future incidents of MDA pre-emption of common-law claims will be 'few' or 'rare.'" 518 U.S. at 508. As Justice Breyer explained, it would make little sense to distinguish between a state agency regulation requiring a particular hearing-aid design and "a state-law tort action that premises liability upon the defendant manufacturer's failure to use [that design] (*say, an award by a jury persuaded by expert testimony that use of a [different design] is negligent.*)" *Id.* at 504 (emphasis added). Under petitioners' position, however, that state-law negligence action would not be preempted, because the common-law tort of negligence is not limited to medical devices intended for human use.

Petitioners rely (Br. 35) on a portion of the *Lohr* majority opinion stating that "the general state common-law requirements in this suit were not specifically developed 'with respect to' medical devices," and therefore were "not the kinds of requirements that Congress and the FDA feared would impede the ability of federal regulators to implement and enforce specific federal requirements." 518 U.S. at 501. In context, that discussion cannot mean that no general common-law requirements are preempted. That conclusion would be inconsistent with Justice Breyer's decisive concurrence.

Instead, the relevant discussion is best read as reflecting the types of federal and state requirements at issue in *Lohr*. The Court was addressing whether "general federal regulations governing the labeling and manufacture of all medical devices" preempted *general* state tort duties. See 518 U.S. at 497 (emphasis added). Here, in contrast, the question is whether FDA's device-specific PMA preempts a State's application of its general tort duties to a specific device. Because this case involves a device-specific federal requirement, it is logical to consider the state requirements at the same level of specificity. Indeed, one must

do so in order to understand the extent to which the state requirements would interfere with the federal ones.

E. The Presumption Against Preemption Does Not Control This Case

Petitioners invoke (Br. 21) the presumption against preemption, asserting this the Court should refuse to find that state tort claims are preempted in the absence of clear evidence of congressional intent. As a majority of this Court recognized in *Lohr*, however, Congress manifested the requisite intent to preempt common-law tort duties that are different from, or in addition to, federal requirements. See p. 16, *supra*. And, as discussed above, the state claims at issue here would clearly interfere with the federal requirements imposed by the PMA process, as they seek to impose liability on respondent for using an FDA-approved design and label.

Moreover, Congress delegated to FDA the responsibility to administer Section 360k's express preemption provision. Accordingly, FDA's judgment that petitioners' claims are preempted is entitled to "substantial weight." *Lohr*, 518 U.S. at 496.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

PAUL D. CLEMENT
Solicitor General

PETER D. KEISLER
Assistant Attorney General

EDWIN S. KNEEDLER
Deputy Solicitor General

DARYL JOSEFFER
*Assistant to the Solicitor
General*

DOUGLAS N. LETTER
SHARON SWINGLE
Attorneys

DANIEL MERON
General Counsel
*Department of Health and
Human Services*

OCTOBER 2007

EXHIBIT G

No. 06-1498

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v.

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BRIEF FOR THE UNITED STATES
AS AMICUS CURIAE SUPPORTING PETITIONERS

DANIEL MERON <i>General Counsel</i>	PAUL D. CLEMENT <i>Solicitor General</i> <i>Counsel of Record</i>
GERALD F. MASOUDI <i>Associate General Counsel</i>	JEFFREY S. BUCHOLTZ <i>Acting Assistant Attorney</i> <i>General</i>
ERIC M. BLUMBERG <i>Deputy Associate General</i> <i>Counsel</i>	EDWIN S. KNEEDLER <i>Deputy Solicitor General</i>
WENDY S. VICENTE <i>Attorney</i> <i>Department of Health and</i> <i>Human Services</i> <i>Washington, D.C. 20201</i>	DARYL JOSEFFER <i>Assistant to the Solicitor</i> <i>General</i>
	DOUGLAS N. LETTER KELSI BROWN CORKRAN <i>Attorneys</i>
	<i>Department of Justice</i> <i>Washington, D.C. 20530-0001</i> <i>(202) 514-2217</i>

QUESTION PRESENTED

Michigan law generally provides that a drug manufacturer is not liable in tort if the federal Food and Drug Administration (FDA) approved the drug, unless the manufacturer “[i]ntentionally withh[eld] from or misrepresent[ed] to the [FDA] information concerning the drug that is required to be submitted under the federal food, drug, and cosmetic act * * * and the drug would not have been approved, or the [FDA] would have withdrawn approval for the drug if the information were accurately submitted.” Mich. Comp. Laws Ann. § 600.2946(5). The question is:

Whether federal law preempts state law to the extent that it requires a court to determine whether a drug manufacturer committed fraud on FDA and whether FDA would have denied or withdrawn approval of a drug but for that fraud.

(I)

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INTEREST OF THE UNITED STATES

This case presents the question whether state law is preempted to the extent it requires a court to determine, as a prerequisite to the award of tort damages, whether a drug manufacturer committed fraud on the Food and Drug Administration (FDA). Resolution of that question will affect FDA's drug approval process and response to fraud on the agency.

STATEMENT

1. Under the Federal Food, Drug, and Cosmetic Act (FDCA or Act), 21 U.S.C. 301 *et seq.*, a drug manufacturer may not market a new drug unless it has submitted a new drug application to FDA and received the agency's approval. 21 U.S.C. 355(a). An application

(1)

must include extensive information about the composition, manufacture, and specification of the drug, any studies of the drug's pharmacological actions and toxicological effects in animals, any studies of the drug's bioavailability and pharmacokinetics in humans, any clinical investigations of the drug, and "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source." 21 C.F.R. 314.50(d); see 21 U.S.C. 355(b)(1). FDA maintains guidance documents on the format and content of applications to assist applicants in their preparation. 21 C.F.R. 314.50.

The applicant may meet with FDA for the purpose of "reaching agreement" on the design and size of clinical trials intended to form the primary basis of an effectiveness claim, 21 U.S.C. 355(b)(5)(B), and to discuss the presentation of supporting information, 21 C.F.R. 314.50(f)(4). Regulations also provide for a conference approximately 90 days after the application is filed and another conference at the conclusion of FDA's review. 21 C.F.R. 314.102(c) and (d). Those conferences provide an opportunity to resolve disagreements over scientific and medical matters, and meetings may be scheduled at other times to resolve disputes. 21 C.F.R. 314.102(e). There may also be communications by telephone and letter. All conversations, letters, and meetings "shall be appropriately documented" in FDA's files. 21 C.F.R. 10.65(e) and (f), 314.102(a).

FDA will approve a new drug application if it determines that the drug meets statutory standards for safety and effectiveness, manufacturing, and labeling. 21 C.F.R. 314.105(e). The regulations state that, while the same statutory standards apply to all drugs, the

wide range of drugs and the variety of their uses “demand flexibility in applying the standards.” *Ibid.* Thus, FDA “is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.” *Ibid.*

After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with use of the drug in humans, 21 C.F.R. 314.80, and must periodically submit any new information that may affect FDA’s previous conclusions about the safety or effectiveness of the drug, 21 C.F.R. 314.81. FDA may withdraw approval of a drug if it finds, among other things, that the drug is unsafe or ineffective. 21 U.S.C. 355(e).

Federal law generally prohibits persons from making false or fraudulent statements of material fact to federal agencies. 18 U.S.C. 1001(a). In addition, the FDCA specifically provides for the withdrawal of approval of a drug if FDA finds that “the application contains any untrue statement of material fact,” 21 U.S.C. 355(e); 21 C.F.R. 314.150(a)(2)(iv), and includes failing to submit required post-market information to FDA among its enumerated prohibited acts, 21 U.S.C. 331(e). The FDCA was recently amended specifically to prohibit the submission of false or misleading clinical trial information. 21 U.S.C. 331(jj)(3); see 42 U.S.C. 282(j)(5)(D).

The FDCA authorizes FDA to investigate violations of the Act, 21 U.S.C. 372, and to pursue a wide range of sanctions for any fraud it uncovers. The agency may withdraw approval of the drug, 21 U.S.C. 355(e), seek injunctive relief in certain circumstances, 21 U.S.C. 332, seize the drug if it is adulterated or misbranded, 21 U.S.C. 334, or pursue criminal prosecution of the manu-

facturer, 21 U.S.C. 333(a); 18 U.S.C. 1001, 1341. As recently amended, the FDCA also gives FDA authority to seek civil monetary penalties for submission of false or misleading clinical trial information. 21 U.S.C. 333(f)(3)(A).

FDA has instituted an administrative policy regarding appropriate measures for responding to false or misleading statements in drug applications. 56 Fed. Reg. 46,191, 46,199-46,200 (1991); see FDA, *Compliance Policy Guide* § 120.100 (1991) <http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg120-100.html>. FDA has also established a general process for citizens to petition FDA to take administrative action, 21 C.F.R. 10.30, which may be invoked by any person who believes a manufacturer has defrauded FDA. There is, however, no private right of action to enforce the FDCA. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4, 352 (2001). The United States has exclusive authority to enforce the Act's provisions, subject only to a limited exception for some actions by States (but not private parties). 21 U.S.C. 337(a).

2. Respondents are Michigan residents who were allegedly injured by Rezulin, a drug marketed by petitioners for the treatment of diabetes. Pet. App. 6a, 30a. FDA approved Rezulin in 1997. Petitioners withdrew it from the market three years later at FDA's request because of adverse side effects in patients taking the drug, see *id.* at 6a-7a, and FDA later withdrew its approval of the drug, 68 Fed. Reg. 1469 (2002).

Respondents filed suit alleging a variety of common-law torts, including breach of express and implied warranties, negligent misrepresentation, defective design, and defective manufacturing. Pet. App. 7a. Michigan law provides:

In a product liability action against a manufacturer or seller, a product that is a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by [FDA], and the drug and its labeling were in compliance with [FDA's] approval at the time the drug left the control of the manufacturer or seller.

Mich. Comp. Laws Ann. § 600.2946(5). That provision does not apply if:

[T]he defendant at any time before the event that allegedly caused the injury * * * [i]ntentionally withholds from or misrepresents to [FDA] information concerning the drug that is required to be submitted under the [FDCA], and the drug would not have been approved, or [FDA] would have withdrawn approval for the drug if the information were accurately submitted.

Ibid. Respondents allege that petitioners knowingly concealed material facts from FDA about the safety and efficacy of Rezulin—including post-approval adverse event reports of liver and heart damage and deaths associated with the drug—which would have prevented approval of Rezulin by FDA or resulted in its earlier removal from the market. Pet. App. 337a, 344a-345a, 353a-354a; J.A. 36, 43. FDA has not made such a determination.

3. The district court dismissed the complaints. Pet. App. 29a-38a. “The question,” explained the court, “is whether the plaintiffs, assuming they have adequately pled fraud on the FDA, should be afforded an opportunity to try to prove it.” *Id.* at 32a. The court answered that question in the negative because it understood this

Court's decision in *Buckman* to hold that "there can be no recovery on a theory of fraud on the FDA." *Id.* at 33a. The court also deferred to the Sixth Circuit's determination in *Garcia v. Wyeth-Ayerst Laboratories*, 385 F.3d 961 (2004), that the fraud-on-the-FDA exception is severable from the remainder of Section 600.2946(5). Pet. App. 33a-34a. Thus, the court concluded, FDA's approval of Rezulin triggered the bar to liability in Section 600.2946(5). *Id.* at 33a-34a, 36a.

4. The court of appeals reversed. Pet. App. 1a-28a. It acknowledged that *Buckman* "held that state 'fraud-on-the-FDA' claims were impliedly preempted by federal law." *Id.* at 4a (quoting *Buckman*, 531 U.S. at 348). But the court concluded that "three differences" between the Michigan statute and the state law in *Buckman* compelled a different result in this case. *Id.* at 18a. First, the court held that a presumption against preemption applies in this case, unlike in *Buckman*, because the "object" of the Michigan statute as a whole is to limit traditional tort liability, not to police fraud on the FDA. *Id.* at 18a-19a. Second, the court reasoned that, while the *Buckman* plaintiffs sought to recover based solely on a showing of fraud on the FDA, respondents assert "traditional" common-law tort duties under which liability is not based solely on fraud on the FDA. *Id.* at 20a-22a. Third, the court stated that, under the Michigan statute but not the state law in *Buckman*, fraud on the FDA is a "defense" rather than an "element" of a plaintiff's cause of action. *Id.* at 24a.

SUMMARY OF ARGUMENT

Michigan law is preempted to the extent it requires courts to determine whether a manufacturer defrauded

FDA and whether FDA would have denied or withdrawn approval of a drug but for the fraud.

A. In *Buckman*, this Court held that a state-law fraud-on-the-FDA claim conflicted with federal law and was therefore preempted. The Court explained that the relationship between a federal agency and the entities it regulates is inherently federal, and that state-law fraud-on-the-FDA claims would give applicants an incentive “to submit a deluge of information that the Administration neither needs nor wants, resulting in additional burdens on the FDA’s evaluation of an application.” 531 U.S. at 351. Because individual drugs differ, the information FDA wants and needs to review a particular drug varies from case to case, based on FDA’s exercise of its expert judgment. Moreover, when FDA concludes that it has been defrauded, it has discretion under the FDCA to pursue those remedies that, in its judgment, best fit a violation. Permitting lay juries to second-guess the adequacy of a manufacturer’s submission to FDA, and to impose damages (including punitive damages) based on their appraisal of any fraud, would interfere with FDA’s exercise of its expert judgment.

B. Justice Stevens concurred in the result in *Buckman* because FDA had not determined “both that fraud ha[d] occurred and that such fraud require[d] the removal of a product from the market.” 531 U.S. at 354. That rationale applies here because, as a predicate for imposing liability, the Michigan statute requires that FDA would have denied or withdrawn approval but for the fraud. Speculation by fact-finders about what FDA would have done in hypothetical circumstances invades the province of the agency. Moreover, a legal standard that turned on such speculation would inevitably lead parties to request burdensome and intrusive discovery

from FDA concerning its approval of a drug, and thereby divert the agency from its core public health mission.

C. The court of appeals attempted to distinguish *Buckman* by asserting that it involved a novel claim alleging only fraud on FDA, whereas this case involves a “traditional” tort. Pet. App. 19a. The Michigan statute is not “traditional,” however, to the extent that, at bottom, it requires a determination of fraud on a federal agency. That inquiry is problematic whether it occurs as part of a stand-alone tort or in determining the applicability of an exception to a limitation. The state statute’s requirement that a plaintiff prove the violation of a traditional tort duty *as well as* fraud on FDA does nothing to diminish the conflicts discussed above. Rather, it means only that those *other* aspects of the state-law claim may not give rise to preemption; it does not reduce the conflict, found in *Buckman*, between federal law and state-law determinations of fraud on FDA.

ARGUMENT

THE MICHIGAN STATUTE IS PREEMPTED UNDER *BUCKMAN* BECAUSE IT REQUIRES A FINDING OF FRAUD ON THE FDA AS A PREREQUISITE TO LIABILITY

Federal law preempts state laws that conflict with federal law, including those state laws that “stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.” *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). This Court held in *Buckman* that “state-law fraud-on-the-FDA claims conflict with, and are therefore impliedly preempted by, federal law.” 531 U.S. at 348. The Michigan statute at issue here is preempted because, just like the fraud-on-the-FDA claims in *Buckman*, it makes liability turn on

whether the defendant withheld information from or made misrepresentations to FDA and whether FDA would have approved or withdrawn its approval of the product if accurate information had been submitted.

A. *Buckman Bars Fraud-On-The-FDA Claims*

The plaintiffs in *Buckman* alleged that the defendant had made false representations to FDA in the course of obtaining pre-market clearance under Section 510(k) of the FDCA, 21 U.S.C. 360(k), to market a medical device that was substantially equivalent to a predicate device already on the market. 531 U.S. at 343, 345-346; see *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 478-480, 492-494 (1996) (describing Section 510(k) pre-market clearance process). The plaintiffs sought damages under state tort law, seeking to establish the elements of common-law fraud by showing that false statements were made to FDA, that FDA relied on those statements in approving the product, and that the false statements caused plaintiffs injury because FDA would not have approved the device (and it therefore would not have been on the market and injured them) in the absence of the statements. See *Buckman*, 531 U.S. at 343, 345-346; *In re Orthopedic Bone Screw Prods. Liability Litig.*, 159 F.3d 817, 826-829 (3d Cir. 1998) (*Orthopedic Litig.*) (discussing Restatement (Second) of Torts § 310, at 103 (1965)), rev'd *sub nom. Buckman, supra*.

The Court first noted that “[p]olicing fraud against federal agencies is hardly a field which the States have traditionally occupied, such as to warrant a presumption against finding federal preemption of a state-law cause of action.” *Buckman*, 531 U.S. at 347 (internal quotation marks and citation omitted). “To the contrary, the relationship between a federal agency and the entity it regu-

lates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law.” *Ibid.* Accordingly, any presumption against preemption was inapplicable. *Id.* at 347-348.

“Given this analytical framework,” the Court held that the fraud-on-the-FDA claims conflicted with federal law and were therefore preempted. *Buckman*, 531 U.S. at 348. That conflict stemmed from the fact that the federal statutory scheme empowers FDA to punish and deter fraud against it, and FDA uses that authority to achieve a “somewhat delicate balance of statutory objectives” that could be skewed by allowing state-law fraud-on-the-FDA claims. *Ibid.* The Court pointed out that the Act and FDA’s implementing regulations impose on applicants various requirements to disclose information to FDA, and at the same time give FDA various tools to detect, deter, and punish false statements made during the approval process—including investigatory powers, a citizen complaint process, criminal prosecutions, injunctive relief, and civil penalties. *Id.* at 348-349; see pp. 3-4, *supra* (discussing FDA’s enforcement authorities with respect to drugs). The Court also noted that “[t]he FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance” with the Act’s provisions. *Id.* at 349 n.4; see 21 U.S.C. 337(a).

The Court explained that the “variety of enforcement options” available exclusively to FDA affords it “flexibility” to make a measured response to suspected fraud against the agency in order to pursue difficult and sometimes competing objectives. *Buckman*, 531 U.S. at 349-350. In the Court’s view, state-law fraud-on-the-FDA claims would “inevitably conflict” with FDA’s responsi-

bility to “police fraud” consistently with its judgment and objectives. *Id.* at 350. Thus, for example, the prospect of fraud-on-the-FDA claims could deter would-be applicants from seeking approval by FDA of beneficial products because disclosure requirements in the approval process could expose them to liability under state law if the disclosures were found to be incomplete. To allow such claims also would cause applicants to fear that their disclosures to FDA would later be judged insufficient by a state court, which would create an incentive to submit much additional information that FDA neither needs nor wants, thereby burdening FDA and delaying the availability of the product. *Id.* at 350-351.

The Court noted that the fraud-on-the-FDA claims were not based on traditional state tort law principles concerning violation of a duty of care owed by the manufacturer to the plaintiffs, such as an alleged failure to use reasonable care in manufacturing the product. Instead, “the fraud claims exist[ed] solely by virtue of the FDCA disclosure requirements,” and “the existence of these federal enactments is a critical element of [plaintiffs’] case.” *Buckman*, 531 U.S. at 352-353. The Court concluded that this sort of litigation “would exert an extraneous pull on the scheme established by Congress, and it is therefore pre-empted by that scheme.” *Id.* at 353.

B. Section 600.2946(5)(a) Is Preempted Under *Buckman*

Although the court of appeals pointed to differences between this case and *Buckman*, see Pet. App. 18a-24a, none of those differences is material. Michigan law explicitly makes liability turn on the very same determination that *Buckman* held to be preempted as a predicate to liability under state law. That inquiry exerts the

same “extraneous pull” here as in *Buckman* (531 U.S. at 353) and is equally preempted.¹

The court of appeals perceived a material difference between the traditional state tort claims at issue here and the fraud-on-the-FDA claims at issue in *Buckman*. Pet. App. 19a-23a. But the claims in *Buckman* were also, at bottom, common-law tort claims, for fraud. See *Orthopedic Litig.*, 159 F.3d at 826-828. What was novel in *Buckman* was not the common-law nature of the underlying tort, but the plaintiffs’ suggestion that they could recover in the absence of any duty between the plaintiffs and defendants if they could show fraud on the FDA. This Court found that theory of recovery preempted by federal law because premising liability on proof of fraud on the FDA impermissibly skewed the federal scheme. The decision proceeds on the assumption that, absent preemption, the conduct would violate a state common-law prohibition on fraud. This case, of course, involves not a plaintiff’s novel effort to make out a common-law fraud action, but a statute that specifies that liability turns on proving fraud on the FDA.

Under Mich. Comp. Laws Ann. § 600.2946(5), in a product liability action against the manufacturer or seller of a drug, the drug is deemed not to be defective or unreasonably dangerous, and the manufacturer or seller is not liable, “if the drug was approved for safety and efficacy by [FDA], and the drug and its labeling

¹ The questions presented in the petition ask only whether state law is preempted to the extent it requires a determination of fraud on FDA. See Pet. (i). The petition does not present the question whether or when FDA’s approval of a drug impliedly preempts traditional state tort claims, and this brief expresses no view on that question. That question is presented in *Wyeth v. Levine*, petition for cert. pending, No. 06-1249 (filed Mar. 12, 2007).

were in compliance with [FDA's] approval at the time the drug left the control of the manufacturer or seller.”² Section 600.2946(5) then specifies an exception that applies if the defendant, at any time before the event allegedly causing the injury, “[i]ntentionally withholds from or misrepresents to [FDA] information concerning the drug that is required to be submitted under the [FDCA], and the drug would not have been approved, or [FDA] would have withdrawn approval for the drug if the information were accurately submitted.” Mich. Comp. Laws. Ann. § 600.2946(5)(a). That provision requires a court entertaining a state-law tort suit to make the same determination that was required and found preempted in *Buckman*. Indeed, the only differences between the inquiry here and in *Buckman* are that here (i) the inquiry is specified by statute, rather than representing an innovative plaintiff’s theory of how to prove a common-law claim, and (ii) the inquiry arises not as a stand-alone sufficient basis for recovery, but as a limit on an immunity from liability. The first difference only strengthens the case for preemption, and the second is not material—the inquiry exerts an “extraneous pull” on the federal scheme no matter how it arises.

To be sure, States generally have authority to carve out exceptions from state-law tort duties, as well as limi-

² While that provision specifies both a state-law rule of decision (that the drug is not defective or unreasonably dangerous) and an immunity from liability by reference to actions of FDA under the FDCA, it is not preempted. Just as it is common and often unproblematic for state law to borrow federal law for a standard of care, see, e.g., *Medtronic*, 518 U.S. at 490; a State’s decision to borrow federal law as a rule of decision or immunity, *vel non*, does not create a preemption issue (although there could be circumstances where such a state-law immunity provision would frustrate the objects of a federal scheme and therefore be preempted).

tations on those exceptions. But contrary to the court of appeals' belief (see Pet. App. 18a-19a), it does not follow that the substantive terms on which Michigan has chosen to carve out such an exception are automatically entitled to a presumption against preemption. In particular, that presumption "is not triggered when the State regulates in an area where there has been a history of significant federal presence," *United States v. Locke*, 529 U.S. 89, 108 (2000), or "where the interests at stake are 'uniquely federal' in nature," *Buckman*, 531 U.S. at 347 (quoting *Boyle v. United Techs. Corp.*, 487 U.S. 500, 504-505 (1988)). Because "the relationship between a federal agency and the entity it regulates is inherently federal," *Buckman* held that "no presumption against pre-emption obtain[ed] in th[at] case." *Id.* at 347, 348.

The court of appeals sought to distinguish *Buckman*'s rejection of a presumption against preemption on the ground that Michigan is seeking to "regulat[e] matters of health and safety." Pet. App. 19a (quoting *Buckman*, 531 U.S. at 348). But again, the question here is not whether traditional tort claims are preempted; it is whether the portion of the Michigan statute that requires a finding of fraud on FDA is preempted. Under *Buckman*, the presumption against preemption has no application to that non-traditional feature of the statute, just as it had no application to the non-traditional means of proving fraud at issue in *Buckman*. 531 U.S. at 347; see, e.g., *Nathan Kimmel, Inc. v. DowElanco*, 275 F.3d 1199, 1205 (9th Cir. 2002).

The court of appeals may have assumed that the presumption against preemption must apply to a cause of action as a whole, as opposed to one aspect of the case, but there is no basis for that assumption. In *Boyle*, for example, this Court held that the presumption against

preemption did not apply to the question of under what circumstances government contractors have a “defense” to state tort suits. 487 U.S. at 504. There, as here, the state tort as a whole related to health and safety, but the presumption against preemption did not apply to a specific issue implicating uniquely federal interests.

As we demonstrate at greater length below, “[g]iven this analytical framework,” *Buckman*, 531 U.S. at 348, Section 600.2946(5)(a) is preempted, just as the fraud-on-the-FDA claims in *Buckman* were preempted.

1. The Michigan statute is preempted because it requires courts and juries, as a predicate to awarding damages, to determine whether an applicant defrauded FDA

a. In *Buckman*, this Court explained that “the relationship between a federal agency and the entity it regulates is inherently federal in character,” and “the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Administration.” 531 U.S. at 347, 348. While *Buckman* involved a medical device, as opposed to a drug, there is no meaningful distinction between drugs and devices in this respect.

As explained above, there is a general prohibition against making false statements to federal agencies. 18 U.S.C. 1001. In addition, the FDCA authorizes FDA to withdraw approval of a drug because of fraud, 21 U.S.C. 355(e), and expressly labels as prohibited conduct the failure to comply with post-approval reporting requirements regarding new safety or efficacy information, 21 U.S.C. 331(e). FDA has authority to investigate suspected fraud by a manufacturer seeking drug approval, 21 U.S.C. 372, and to pursue a wide range of sanctions for any fraud it uncovers, including withdrawal of approval, 21 U.S.C. 355(e), injunctive relief, 21 U.S.C. 332,

seizure, 21 U.S.C. 334, civil monetary penalties, 21 U.S.C. 333(f)(3)(A), and criminal prosecution, 21 U.S.C. 333(a); 18 U.S.C. 1001, 1341. “FDA thus has at its disposal a variety of enforcement options.” *Buckman*, 531 U.S. at 349 (footnote omitted).

FDA uses its authority “to punish and deter fraud against the Administration, and * * * to achieve a somewhat delicate balance of statutory objectives,” and this “balance * * * can be skewed by allowing fraud-on-the-FDA claims under state tort law.” *Buckman*, 531 U.S. at 348. For example, *Buckman* observed that the prospect of fraud-on-the-FDA claims could deter manufacturers from even submitting products for approval because the federal requirements for disclosure to FDA could expose them to state tort liability. *Id.* at 350-351. Also, “fraud-on-the-FDA claims would * * * cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court.” *Id.* at 351. Applicants would then have an incentive to submit information that FDA neither wants nor needs, resulting in additional burdens on FDA’s evaluation of an application and delays in the approval process and the introduction of the product into the market. *Ibid.*

Of course, Michigan law also requires proof of violations of traditional state-law tort duties owed by a manufacturer to a user of the product that exist independently of the federal regulatory scheme. Issues concerning fraud on FDA—and what FDA would have done if accurate information had been submitted—arise in connection with an immunity from traditional liability that the State has elected to afford. But the conflict is the same as with the stand-alone fraud-on-the-FDA claims in *Buckman*, because in both instances damages may be

awarded only if a court finds that information was withheld or misrepresented to FDA and that FDA would have disapproved the product or withdrawn it sooner if it had received accurate information. See pp. 27-29, *infra*.³

b. Section 600.2946(5)(a) also threatens to upset the balance struck by the FDCA and implementing regulations in affording FDA broad discretion to oversee the application process and respond to misrepresentations or omissions of information. The regulations set forth detailed requirements concerning the information manufacturers must submit to the agency, both during the approval process and after a drug has been marketed. See 21 C.F.R. 314.50, 314.80, 314.81; pp. 1-3, *supra*. Those regulations seek to clarify the requirements for manufacturers while relieving the agency of the burden of evaluating unnecessary information.

Because individual drugs differ, the information FDA needs in order to review a particular drug will vary from case to case. Cf. *Merck KGaA v. Integra Lifescis. I, Ltd.*, 545 U.S. 193, 207 (2005) (discussing “the uncertainties that exist with respect to * * * what research

³ In *Buckman*, the Court focused on the adverse impact that fraud-on-the-FDA claims could have on the Section 510(k) pre-market clearance process for medical devices, which is designed to be comparatively streamlined and speedy. See 531 U.S. at 348-351. This case involves the submission of new drug applications, which entails a far more comprehensive review than under Section 510(k). The preemption question under *Buckman* should be answered as a general matter, however, and should not turn on the procedures that are applicable to the particular product under the FDCA. The basic point of *Buckman*—that FDA is charged with striking a balance between keeping unsafe products off the market and making efficacious products available to patients and doctors that should not be skewed by state law—applies to all of FDA’s approval processes under the FDCA.

to include in” a new drug application). FDA “is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.” 21 C.F.R. 314.105(c). Because of the complexity of the analysis, an applicant may request a meeting with FDA for the purpose of “reaching agreement” on the design and size of the drug’s clinical trials, 21 U.S.C. 355(b)(5)(B), and to discuss the presentation of information, 21 C.F.R. 314.50(f)(4). FDA “usually communicates often with sponsors about scientific, medical, and procedural issues that arise during the review process. Communications may take the form of telephone conversations, letters, faxes or meetings.” FDA, *The CDER Handbook* 24 (1998) <<http://www.fda.gov/cder/handbook/handbook.pdf>>. Permitting lay juries to second-guess the adequacy of a manufacturer’s submissions of information to FDA in that ongoing process would interfere with FDA’s expert judgment on what information it wants and needs.

Moreover, in situations where FDA concludes that omissions or misrepresentations occurred, the FDCA gives FDA “complete discretion” to pursue those remedies that, in the agency’s judgment, best fit a violation and the overall purposes of the Act. *Heckler v. Chaney*, 470 U.S. 821, 835 (1985). Notwithstanding fraud, FDA may decide that a drug’s health benefits counsel against removing it from the market or imposing a severe administrative penalty, and that other sanctions are more appropriate. Awards of damages (including punitive damages) based on state-law determinations of fraud on

the FDA would interfere with FDA's determination of the appropriate remedy.⁴

In these respects, Section 600.2946(a)(5) "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Davidowitz*, 312 U.S. at 67, in conferring authority and discretion on FDA to tailor the application process and choose the appropriate remedies for violations of disclosure requirements. Cf. *Crosby v. National Foreign Trade Council*, 530 U.S. 363, 372-374 (2000).

If a State established its own administrative agency to monitor whether regulated entities were withholding or misrepresenting information to FDA, and to impose monetary remedies upon a finding that FDA would have acted differently if accurate information had been submitted, the conflict between that state law and the federal interests would be manifest. As *Buckman* reflects, there likewise is a conflict when monetary remedies are imposed in state-law tort litigation on that basis.

2. The Michigan statute is preempted because it requires courts to determine whether FDA would have denied or withdrawn approval if it had received accurate information

a. There is an additional reason why the Michigan statute is preempted. As the *Buckman* concurrence

⁴ Some state statutes condition the availability of *punitive* damages on a finding that information was withheld from or misrepresented to FDA. See Pet. Br. 11-12 & n.6. Conditioning the availability of punitive damages on that basis would have a particularly acute impact on FDA's oversight of the approval process and selection of remedies for misrepresentation. Cf. *Credit Suisse Sec. (USA) LLC v. Billing*, 127 S. Ct. 2383, 2396 (2007) (noting that threat of treble damages would make it impossible for the agency to police fine distinctions between forbidden conduct and closely related conduct that was affirmatively encouraged).

explained, “an essential link in the chain of causation that [a plaintiff] must prove in order to prevail is that, but for [defendant’s] fraud, the allegedly defective [product] would not have reached the market.” 531 U.S. at 353 (Stevens, J., concurring in the judgment). In the absence of a determination by FDA “both that fraud has occurred and that such fraud requires the removal of a product from the market,” plaintiffs could not “establish a necessary element of their claim.” *Id.* at 353 n.1, 354. Without such action by FDA, the state law would require a difficult inquiry into “a counterfactual situation” and “second-guessing [of] the FDA’s decisionmaking” by state courts and juries. *Id.* at 354.

This Court has long accorded preemptive effect to a federal administrative decision that has neither been rescinded by the agency nor set aside by a federal court in accordance with the procedures for review established by Congress. In *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571, 578-579 (1981) (*Arkla*), for example, this Court held that a state contract action was preempted by the Federal Power Commission’s (FPC’s) approval of a filed rate different from the one provided by contract. Although the state supreme court had determined that the FPC would have approved the higher rate as reasonable had the circumstances of the case been brought to its attention, this Court held that “the Commission alone is empowered to make that judgment, and until it has done so, no rate other than the one on file may be charged.” *Id.* at 581. By awarding damages based on a determination of what the FPC *might* have done, the state court “usurped a function that Congress has assigned to a federal regulatory body.” *Id.* at 582;

see *Chicago & N.W. Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311, 326 (1981).⁵

Like the state law in *Buckman*, the Michigan statute requires a determination that “the drug would not have been approved, or the [FDA] would have withdrawn approval for the drug if the information were accurately submitted.” Mich. Comp. Laws Ann. § 600.2946(5)(a). FDA has never made such a determination. To be sure, three years after FDA approved the application for Rezulin, it asked petitioners to take the drug off the market, and FDA later withdrew its approval for safety-related reasons. See Pet. App. 6a-7a; 68 Fed. Reg. 1469 (2002). FDA did not, however, rely on a finding of fraud in doing so. See 68 Fed. Reg. at 1469. Indeed, when FDA withdraws approval of a drug, it normally does so for reasons other than fraud, including, as with Rezulin, that newly available information revealed that the drug was not as safe or effective as the agency previously thought. See 21 U.S.C. 355(e). Therefore, federal law precludes a state rule—whether as an element of a claim or of a defense—that turns on whether FDA would have denied approval or withdrawn it sooner if it had received accurate information.

b. As the *Buckman* concurrence suggests, and the district court stressed, a contrary result would not only entail intrusive “second-guessing [of] the FDA’s decisionmaking,” it would also “overburden[] its personnel.” 531 U.S. at 354; see Pet. App. 35a-36a; see also U.S. Amicus Br. at 28-30, *Buckman*, *supra*. Parties would

⁵ The *Arkla* Court “save[d] for another day the question whether the filed rate doctrine applies in the face of fraudulent conduct.” 453 U.S. at 583 n.13. The *Buckman* concurrence took the next step by recognizing that only the federal agency can determine whether it was defrauded. See 531 U.S. at 353-354 & n.1.

likely seek discovery from FDA concerning whether a manufacturer misrepresented or withheld information that it was required to submit to FDA, as well as discovery concerning the agency's internal deliberations, including agency officials' states of mind and the courses of action they might have taken under various hypothetical scenarios. The United States' position is that employees of the federal government are immune from third-party subpoenas issued in private litigation, that testimony must be sought under an agency's Touhy regulations, see generally *United States ex rel. Touhy v. Ragen*, 340 U.S. 462 (1951), and that an agency's denial of a request for testimony by agency employees is subject to review only in federal court and only under the arbitrary or capricious standard of the Administrative Procedure Act (APA), 5 U.S.C. 706(2)(A). The lower federal courts, however, have taken divergent views on issues concerning third-party subpoenas when issued by a federal court to federal employees. Compare, e.g., *Comsat Corp. v. National Sci. Found.*, 190 F.3d 269, 277-278 (4th Cir. 1999) (applying APA standard), with *Exxon Shipping Co. v. United States Dep't of Interior*, 34 F.3d 774, 778-780 (9th Cir. 1994) (holding that agency is protected only by court's discretion to limit discovery under Federal Rules of Civil Procedure 26 and 45).

Nor would the undesirable consequences abate if the courts ultimately accepted the government's position on when its officials can be required to testify. Parties would still be free to challenge any refusal to testify under the APA. In one recent products liability class action, *Walson v. Merck & Co.*, No. 3:04-cv-00027-GPM-DGW (S.D. Ill.), FDA devoted approximately 1,300 employee hours to producing approximately 40,000 pages of documents in response to a third-party subpoena.

Private litigation such as this would divert FDA's resources and create a substantial potential for distorting its mission.

c. While an FDA decision finding fraud and withdrawing its approval of the product would overcome pre-emption under the rationale of the *Buckman* concurrence, a rule that made preemption turn on the presence or absence of a decision by FDA could create its own potential for interference with the federal scheme. See 12/4/2000 Oral Arg. Tr. 20-21, 23-25, *Buckman, supra* (argument of the United States).⁶

The federal government alone has responsibility to determine the appropriate remedy under the FDCA when it approved a product and later learned of misrepresentations that might have led it not to approve the product. See pp. 18-19, *supra*. The addition of potential damages liability in an uncertain amount under state law to the consequences ensuing from FDA's own remedy under the FDCA would skew FDA's exercise of its discretion under the FDCA. Cf. *Credit Suisse Sec. (USA) LLC v. Billing*, 127 S. Ct. 2383, 2396 (2007). In addition, if FDA were the gatekeeper for private tort liability, it could anticipate numerous petitions filed by prospective tort plaintiffs urging the agency to make a finding of fraud. The disposition of such petitions might prove every bit as burdensome for the agency as state-court litigation concerning whether FDA was defrauded. Par-

⁶ We note that, in a preamble to a recent rule, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3936 (2006), FDA provided examples of state-law claims that in its view are preempted under current doctrine by its approval of a drug, including some claims for failure to warn "unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning."

ties would presumably seek extensive information from FDA, pursuant to the agency's Touhy regulations and the Freedom of Information Act, 5 U.S.C. 552, to support or defend against such an assertion. And it could be difficult for FDA to respond to numerous such petitions within the 180-day regulatory timeframe. See 21 C.F.R. 10.30(e)(2).

While FDA takes suggestions of fraudulent representations very seriously, it does not have a process for considering allegations or making explicit findings of fraud in the abstract. Citizen petitions must seek specific types of administrative action, such as withdrawal of a drug's approval, not merely a finding of fraud. See 21 C.F.R. 10.30(b). And even if FDA chose to grant such a petition, it would not necessarily premise the withdrawal on a formal finding of fraud. When FDA suspects fraud, it often reaches a settlement with the applicant in which the applicant pays a fine or takes corrective action (such as changes in labeling) without admitting liability. Thus, FDA does not presently have a system to process routine requests to make findings of fraud in service of private litigation, and any expectation that it do so "would exert an extraneous pull" on FDA, *Buckman*, 531 U.S. at 353, and divert its resources away from its core public health mission.⁷

⁷ When necessary and appropriate, the government has secured formal relief, including criminal convictions, against drug or device manufacturers who defrauded the agency. See, e.g., FDA, *Enforcement Story* (last modified Aug. 7, 2003) <http://www.fda.gov/ora/about/enf_story/archive/2001/ch6/default.htm> (corporate officers sentenced to 15 months of imprisonment for fraudulent submission to FDA); John Henkel, *Investigators' Reports*, FDA Consumer, Nov.-Dec. 1997, at 38 (drug company criminally convicted for, among other things, submitting false statements to FDA in annual reports for approved drugs).

**3. FDA's position that the Michigan statute conflicts
with federal law is entitled to deference**

Any lingering doubt should be resolved by deference to FDA's expert judgment. Congress delegated to FDA authority to administer the process of approving drugs for marketing, monitoring the safety and effectiveness of drugs after they have been marketed, deciding whether to withdraw approval, and determining whether the agency was defrauded and, if so, what remedies to impose. See pp. 1-4, *supra*. As this Court explained in *Medtronic*, FDA's role in administering the drug-approval process makes it "uniquely qualified to determine whether a particular form of state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" 518 U.S. at 496 (quoting *Davidowitz*, 312 U.S. at 67); see *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861, 883 (2000).

**C. The Court Of Appeals' Grounds For Distinguishing This
Case From *Buckman* Are Without Merit**

The court of appeals sought to distinguish *Buckman* on the ground that it involved a novel claim alleging only fraud on the FDA, whereas, the court of appeals asserted, this case involves a "traditional" tort to which fraud on the FDA is relevant to a defense. Pet. App. 19a-24a. None of the asserted distinctions embedded in the court's description detracts from the fact that the Michigan statute makes liability turn on the very determination that *Buckman* bars.

1. The court of appeals reasoned that respondents' claims are "premised on traditional [tort] duties," not "a newly-concocted duty between a manufacturer and a federal agency." Pet. App. 20a. But there is no material difference between the claims here and in *Buckman*.

Respondents allege claims that *sound* traditional, such as negligence, defective design, and breach of warranty. See *id.* at 7a. But although the fraud-on-the-FDA claim in *Buckman* sounded novel, at bottom, it was a plaintiff's innovative effort to make out a common-law fraud action (against a defendant other than a manufacturer). And, of course, preemption resulted not from the novelty of the claim, but from the fact that liability turned on an inquiry that frustrated the federal scheme. Michigan law is no different.

Under the Michigan statute, “a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable,” if, among other things, FDA approved the drug and was not defrauded into doing so. Mich. Comp. Laws Ann. § 600.2946(5). That is not a “traditional” law, and more to the point it calls for the same problematic inquiry that was at issue in *Buckman*. Genuinely traditional tort suits are not preempted under *Buckman* because they do not require a determination that a federal agency was defrauded. But Section 600.2946(5) is preempted precisely because it requires such a finding as a predicate for liability.

Thus, the question is not whether a claim relies on a traditional-*sounding* duty, but whether the particular suit interferes with a federal prerogative. See, e.g., *Sears, Roebuck & Co. v. Stiffel Co.*, 376 U.S. 225, 231 (1964) (“Just as a State cannot encroach upon the federal patent laws directly, it cannot, under some other law, such as that forbidding unfair competition, give protection of a kind that clashes with the objectives of the federal patent laws.”); see also *American Airlines, Inc. v. Wolens*, 513 U.S. 219, 227-228 (1995) (state fraud claims); *Arkla*, 453 U.S. at 573, 580-582 (breach-of-con-

tract action); *Kalo Brick*, 450 U.S. at 323-324, 326-327 (negligence claim).

2. The court of appeals also emphasized that “proof of fraud against the FDA [wa]s alone sufficient to impose liability” in *Buckman*, whereas here, a plaintiff must prove more, such as negligence. Pet. App. 20a-21a. The court of appeals also expressed the view that respondents’ traditional tort claims “cannot reasonably be characterized as a state’s attempt to police fraud against the FDA.” *Id.* at 18a. But it is the Michigan statute, not traditional tort claims, that is the proper focus of the preemption inquiry, just as *Buckman* focused on the novel fraud-on-the-FDA theory, rather than a common-law fraud action in the abstract.

In *Buckman*, the Court characterized the claims as “[p]olicing fraud” on the FDA, 531 U.S. at 347, in “inevitable[e] conflict” with “FDA’s responsibility to police fraud” itself, *id.* at 350. The FDCA “leaves no doubt that it is the Federal government rather than private litigants who are authorized to file suit for noncompliance,” *id.* at 349 n.4, and allowing private damage actions based solely on violations of the FDCA would conflict with Congress’s decision not to provide a private right of action under the FDCA, see *Merrell Dow*, 478 U.S. at 810, 812. While respondents’ tort claims, in the abstract, may not be directed at “policing fraud” against FDA, the overlay of Section 600.2946(5)(a) on those tort claims results in the same impermissible intrusion into FDA’s oversight of the approval process and its exercise of enforcement discretion as the specific claims in *Buckman*.

Moreover, a plaintiff’s need to prove something *in addition to* fraud on the FDA, such as negligence—as well as causation, injury, and damages, which the

Buckman plaintiffs also had to prove—does nothing to eliminate the conflict that results from a state-law requirement that a court make the determination that *Buckman* prohibits as a predicate for liability.⁸ Although “[i]n some cases * * * [an] entire body of state law * * * conflicts and is replaced by federal rules,” “[i]n others, the conflict is more narrow, and only particular elements of state law are superseded.” *Boyle*, 487 U.S. at 508. In *Boyle*, for example, plaintiffs brought a state tort suit for defective design and repair of a Marine helicopter that had crashed, killing the servicemen inside. *Id.* at 502. This Court did not hold that the state tort claims were preempted in their entirety, but instead held that state law was preempted on the specific question of under what circumstances government contractors are immune from state tort liability. *Id.* at 512.

Similarly, in *Arkla*, the state court determined both that the federal commission would have approved a different rate *and* that the plaintiff was entitled to that rate under state contract law. 453 U.S. at 573-575. In that circumstance as in this one, proving an additional element (breach of contract) did not eliminate the conflict. See *Howard v. Lyons*, 360 U.S. 593, 597 (1959) (state tort claim subject to specific federal privilege defense). And, of course, in *Buckman*, the Court did not invalidate any aspect of the common law of fraud beyond invalidating the plaintiffs’ fraud-on-the-FDA theory.

⁸ Indeed, there may be substantial overlap between the common-law duty and the inquiry into whether FDA would have denied or withdrawn approval but for the fraud. Products liability claims typically require a showing that a product is unreasonably dangerous, see, e.g., *Crews v. General Motors Corp.*, 253 N.W.2d 617, 619 (Mich. 1977), and FDA’s decision to approve a drug likewise turns in large part on whether the drug is safe, 21 U.S.C. 355(d).

And the problem in *Buckman* was that the plaintiffs' theory required them to prove fraud on the FDA, *not* the happenstance that plaintiffs' theory required them to prove little else.

Consistent with these principles, other courts of appeals have recognized that *Buckman* is not limited to circumstances where liability is premised *solely* on fraud on a federal agency. See, e.g., *Garcia v. Wyeth-Ayerst Labs.*, 385 F.3d 961, 966 (6th Cir. 2004) (Section 600.2946(5)(a) preempted); *Kimmel*, 275 F.3d at 1206 (preemption because fraud on federal agency was a "critical element of [plaintiff's] state-law case").⁹

3. The court of appeals "presum[ed]" that, "in most states in the country," evidence of fraud on a regulatory agency is "permitted but not conclusive." Pet. App. 25a. Further presuming that federal law does not preempt the introduction of evidence of fraud on FDA in such circumstances, the court reasoned that "the incentive to supply additional data to FDA under the Michigan law before us is no greater than the incentive that exists whenever evidence of what a company submitted, or failed to submit, to the FDA is admissible and probative of liability." *Ibid.* Thus, the court of appeals concluded, the Michigan statute does not conflict with federal law. *Ibid.*

That analysis is flawed. At the outset, it assumes that juries generally consider evidence of fraud on fed-

⁹ If the exception to immunity is not severable under state law, Section 600.2946(5) is invalid as a whole, and petitioner has no state-law immunity based on FDA's approval of the drug. The United States takes no position on that state-law question because severability analysis is not relevant to the federal preemption question presented here, and the court of appeals did not reach it. Cf. *Garcia*, 385 F.3d at 966-967 (holding that the fraud-on-the-FDA provision is severable from the remainder of Section 600.2946(5)). Cf. p. 12 n.1, *supra*.

eral agencies. It is true that, under the Restatement (Third) of Torts: Products Liability § 4(b) (1998) (Restatement), a jury may consider evidence of “a product’s compliance with an applicable product safety statute or administrative regulation” as part of a broader inquiry into whether a product is defective, but that such evidence is entitled to “little or no weight” if “the deliberative process that led to the safety standard with which the defendant’s product complies was tainted by the supplying of false information to, or the withholding of necessary and valid information from, the agency that promulgated the standard or certified or approved the product.” *Id.* § 4 cmt. e.

In practice, however, relatively few reported cases have involved evidence of fraud on an agency under the Restatement approach (and the court of appeals cited none). And the Restatement emphasizes that “questions of federal preemption are beyond [its] scope.” Restatement § 4 cmt. e. At a minimum, there is less incentive to deluge FDA with information in light of the Restatement than in light of the decision below because the question of fraud on the FDA is not dispositive under the Restatement. The conflict with federal law also is not as sharp because the Restatement approach does not require a finding of fraud or that the federal agency would have disapproved the product in the absence of fraud. But regardless of how preemption and related issues might play out in *that* context, there is clearly preemption where, as here and in *Buckman*, findings that FDA was defrauded and that FDA would have disapproved or withdrawn its approval of a product in the absence of fraud are legally mandated predicates for recovery.

4. The court of appeals also found it relevant that fraud on the FDA is not an “element” of respondents’ claims, but instead rebuts a defendant’s reliance on the “affirmative defense” of FDA approval. Pet. App. 23a-24a. That distinction, too, is immaterial.

At the outset, it is not clear that fraud on the FDA is only relevant to an affirmative defense. Section 600.2946(5)(a) states that “a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable,” if, among other things, FDA approved the drug and was not misled. The defective or unreasonably dangerous nature of a product is ordinarily an element of a products liability claim. See, e.g., *Crews v. General Motors Corp.*, 253 N.W.2d 617, 619 (Mich. 1977). And respondents’ complaints affirmatively allege fraud on the FDA. Pet. App. 337a, 344a, 354a; J.A. 33, 36, 43. The court of appeals relied on the Michigan Supreme Court’s description of the statute as providing an “absolute defense.” Pet. App. 23a (quoting *Taylor v. Smithkline Beecham Corp.*, 658 N.W.2d 127, 131 (2003)). But *Taylor* did not fully consider whether Section 600.2946(5) is relevant to a plaintiff’s *prima facie* case or an affirmative defense—or whether the plaintiff bears the burden of proof on the exception once the defendant invokes the general rule of non-liability—because the issue there was whether the statute is constitutional. See *Taylor*, 658 N.W.2d at 137.

In any event, there is no reason why a state-law label would matter for conflict preemption purposes. All that matters is that the state statute requires a determination of fraud on FDA as a predicate to liability, and therefore conflicts with federal law under *Buckman*. Whatever label Michigan might place on the inquiry, “courts would have to engage in the [same] intrusive

inquiry which * * * is forbidden." *Michael v. Shiley, Inc.*, 46 F.3d 1316, 1329 (3d Cir.), cert. denied, 516 U.S. 815 (1995). Any "attempt to reexamine the FDA's approval under state law standards, however pleaded, is pre-empted." *Ibid.*

The court of appeals appears to have been influenced by the fact that Section 600.2946(5), as a whole, benefits drug manufacturers by providing a defense to an otherwise traditional tort claim. See Pet. App. 18a-19a. While that question may have some relevance to the state-law severability question that is not before the Court, see p. 29 n.9, *supra*, it does not affect the reality that liability ultimately turns on the fraud-on-the-FDA inquiry and that inquiry is preempted under *Buckman*. Depending on the answer to the severability question, the finding of preemption may ultimately help the plaintiffs or the defendants. But the preemption inquiry does not turn on whether the law is "pro-defendant." In *Mackey v. Lanier Collection Agency & Service, Inc.*, 486 U.S. 825, 830 (1988), the Court held that the Employee Retirement Income Security Act of 1974, 29 U.S.C. 1001 *et seq.*, preempted a state statute that singled out federal benefit plans for *favorable* treatment because "[l]egislative 'good intentions' do not save a state law" that intrudes on the federal sphere. Preemption does not exist to help particular parties; it exists to protect the federal sphere from interference by the States.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

DANIEL MERON <i>General Counsel</i>	PAUL D. CLEMENT <i>Solicitor General</i>
GERALD F. MASOUDI <i>Associate General Counsel</i>	JEFFREY S. BUCHOLTZ <i>Acting Assistant Attorney General</i>
ERIC M. BLUMBERG <i>Deputy Associate General Counsel</i>	EDWIN S. KNEEDLER <i>Deputy Solicitor General</i>
WENDY S. VICENTE <i>Attorney Department of Health and Human Services</i>	DARYL JOSEFFER <i>Assistant to the Solicitor General</i>
	DOUGLAS N. LETTER
	KELSI BROWN CORKRAN <i>Attorneys</i>

NOVEMBER 2007

EXHIBIT H

No. 06-3107

IN THE UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

JOSEPH C. COLACICCO, Individually and as Executor of the
Estate of Lois Ann Colacicco, Deceased,
Plaintiff-Appellant,

v.

APOTEX, INC.; APOTEX CORP., as Subsidiary of Apotex, Inc.;
SMITHKLINE BEECHAM, d/b/a/ GlaxoSmithKline,
Defendants-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

BRIEF OF THE UNITED STATES AS AMICUS CURIAE
IN SUPPORT OF DEFENDANTS-APPELLEES

DANIEL MERON
General Counsel
Department of Health and
Human Services

SHELDON T. BRADSHAW
Chief Counsel

ERIC M. BLUMBERG
Deputy Chief Counsel

JENNIFER E. CARUSO
Associate Chief Counsel
Food and Drug Division
Department of Health and
Human Services
Office of General Counsel

PETER D. KEISLER
Assistant Attorney General

C. FREDERICK BECKNER III
Deputy Assistant Attorney
General

PATRICK L. MEEHAN
United States Attorney

DOUGLAS N. LETTER
(202) 514-3602
SHARON SWINGLE
(202) 353-2689
Attorneys, Appellate Staff
Department of Justice
Civil Division
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

IN THE UNITED STATES COURT OF APPEALS
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ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

BRIEF OF THE UNITED STATES AS AMICUS CURIAE
IN SUPPORT OF DEFENDANTS-APPELLEES

INTERESTS OF THE UNITED STATES

Pursuant to 28 U.S.C. § 517 and Federal Rule of Appellate Procedure 29(a),
the United States files this brief as amicus curiae in support of affirmance.

The plaintiff in this litigation seeks to impose tort liability on drug manufacturers for failure to warn of an alleged danger, notwithstanding the Food and Drug Administration's repeated determination during the relevant period that the existing scientific knowledge did not support such a warning. Although the Food and Drug Administration (FDA) has the deepest sympathy for the plaintiff because of the death of his wife, it is vital to ensure that state tort law does not

undermine the agency's statutory authority and its ability to protect the public health by prohibiting the false or misleading labeling of drug products. To base a tort judgment on drug manufacturers' failure to warn in October 2003 of an association between adult use of paroxetine hydrochloride and suicide or suicidality, despite FDA's judgment at that time that there was not reasonable scientific evidence of such an association, would be to demand a warning statement that would have been false or misleading, and thus contrary to federal law. In such a case, as the district court properly recognized, federal law must prevail.¹

STATEMENT

A. Statutory and Regulatory Framework.

1. FDA is the expert federal agency charged by Congress in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (FDCA), with regulating the manufacture, sale, and labeling of prescription drug products.² In particular,

¹ In appearing as amicus curiae in this litigation, the Government has limited its analysis to the application of federal preemption to the failure-to-warn claim arising out of defendants' failure in October 2003 to warn on the drug labeling for their products of an asserted association between paroxetine hydrochloride and adult suicide or suicidality. Contrary to the plaintiff's assertion (at Br. 3-4), the Government has not taken a position on the plaintiff's other claims.

² FDA is a component of the United States Department of Health and Human Services (HHS). The Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (continued...)

FDA has been charged with ensuring that drugs sold in the United States are safe and effective, *id.* § 355(d) and § 393(b)(2)(B), and that they are not misbranded, *id.* §§ 331(a), (b), and (k), 352, and 321(n).

In order to obtain FDA approval to market a new innovator drug, a manufacturer must submit a New Drug Application. *See* 21 U.S.C. § 355(b). The manufacturer must provide full reports of investigations conducted to determine the safety and effectiveness of the drug. *Id.* § 355(b)(1)(A). The manufacturer must also provide “specimens of the labeling proposed to be used for such drug.” *Id.* § 355(b)(1)(F). FDA will deny the application if the manufacturer does not provide, *inter alia*, adequate tests to show that the “drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.” *Id.* § 355(d)(1).

Once an innovator drug has been approved for sale, a drug manufacturer may seek approval under the FDCA to market a generic form of that drug. The approval process for a generic drug is abbreviated, and does not require the manufacturer to show independent clinical evidence of efficacy or safety. Instead,

²(...continued)
seq. (FDCA), vests regulatory and enforcement authority in the Secretary of Health and Human Services. The Secretary has delegated this authority to the Commissioner of FDA. FDA Staff Manual Guides, Vol. II, § 1410.10 (available at http://www.fda.gov/sing/1410_10.html).

the manufacturer must show that the generic drug generally has the same active ingredients as the innovator drug and is bioequivalent to that drug. *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iv). The manufacturer must also show that the “labeling proposed for the [generic] drug is the same as the labeling approved for” the innovator drug. *Id.* § 355(j)(2)(A)(v). The only labeling changes permitted to be made are changes to reflect a different manufacturer or that the generic drug has “a different active ingredient” or a different “route of administration, dosage form, or strength.” *Id.* § 355(j)(2)(A), (j)(2)(C); *see also* 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7).

Following FDA approval to market a drug, manufacturers are subject to continuing obligations under the FDCA. *See* 21 U.S.C. § 355(k); 21 C.F.R. §§ 314.80, 314.98. A manufacturer must keep a record of any “adverse event associated with the use of a drug in humans, whether or not considered drug related,” and must periodically report these adverse events to FDA. 21 C.F.R. §§ 314.80(a), (c), 314.98(a). For adverse events that are “serious and unexpected,” the manufacturer is required to report the event to FDA within 15 days, and to conduct an investigation and provide follow-up information to the agency. *Id.* §§ 314.80(c)(1), 314.98(a).

2. The preemption issue raised in this appeal implicates the labeling provisions of the FDCA, as implemented by FDA. Under the FDCA, a drug is

unlawfully misbranded when its labeling is false or misleading in any particular, or does not provide adequate directions for use or adequate warnings against any use dangerous to health. *See* 21 U.S.C. § 331(a), (b), and (k); *id.* § 352(a), (f), (j); *id.* § 321(n). A prescription drug label satisfies federal requirements if it gives physicians and pharmacists sufficient information, including indications for use and “any relevant hazards, contraindications, side-effects, and precautions,” to allow those medical professionals to “use the drug safely and for the purposes for which it is intended * * *.” 21 C.F.R. § 201.100(c)(1). Under federal law, therefore, the evaluation of a drug’s safety and effectiveness is inextricably linked with the drug labeling. *See also* 50 Fed. Reg. 7452, 7470 (1985) (“Drug labeling serves as the standard under which FDA determines whether a product is safe and effective.”).

FDA regulations set forth specific requirements for prescription drug labeling. *See* 21 C.F.R. Part 201, Subparts A, B, and G. Prescription drug labels must contain “a summary of the essential scientific information needed for the safe and effective use of the drug,” which includes indications for use as well as a description of “clinically significant adverse reactions” and “other potential safety hazards” associated with use of the drug. 21 C.F.R. § 201.57(c)(6)(i). The labeling regulations are designed to require warnings of all known risks that are based on reliable scientific evidence. *See id.* (requiring as a condition of warning

that there be “reasonable evidence of a causal association” between use of a drug and “a clinically significant hazard”).

As noted, applications for both innovator drugs and generic drugs must include copies of the proposed labeling for FDA’s review and approval. For innovator drugs, FDA considers evidence submitted by the applicant, as well as other relevant scientific information, to determine whether the label is accurate, truthful, not misleading, and adequate. FDA and drug manufacturers discuss in detail the proposed drug labeling, including the various warnings to be placed on the product. Based on the known scientific evidence, appropriate warnings are drafted that identify established risks while avoiding inadequately substantiated risks, the mention of which could improperly deter use of the drug and result in harm to patients who unnecessarily forego medication. When FDA approves a new drug application for an innovator drug, it also approves the precise final version of the drug labeling. *See* 21 C.F.R. § 314.50(e)(2)(ii), (l)(1)(i); *id.* § 314.105(b).

For generic drugs, FDA confirms as a condition of approval that, with exceptions not applicable here, the labeling is the same as the labeling approved for the innovator drug of which the drug is a generic form. 21 U.S.C. § 355(j)(4)(G). As noted, generic drug manufacturers are required to use labeling

that is, for relevant purposes, identical to the approved labeling for the innovator drug.

A manufacturer may not deviate from FDA-approved product labeling except in limited circumstances set forth in FDA regulations. If the manufacturer of an innovator drug wishes to add or strengthen a warning statement on the approved labeling, the manufacturer may provide FDA with a supplemental submission, providing a full explanation of the basis for the proposed change. *See* 21 C.F.R. § 314.70(c)(1), (3), (6)(iii)(A).³ If the FDA has not rejected the supplement within 30 days after its submission, the manufacturer may distribute the drug with the new labeling — although FDA can reject the change even after this date, and can order the manufacturer to cease distributing the drug with the new labeling. *See* 21 C.F.R. § 314.70(c)(7).

For a generic drug manufacturer, there is no statutory or regulatory provision permitting a labeling change to be made without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. *See* 21 C.F.R. § 314.150(b)(10); *see also* 57 Fed. Reg. 17,950, 17,953, 17,961 (1992). If a generic drug manufacturer believes

³ Indeed, if the drug manufacturer has “reasonable evidence of an association of a serious hazard with a drug,” the manufacturer has an obligation to seek FDA approval for a labeling change, in order to add a warning of the new potential hazard. *See* 21 C.F.R. § 201.80(e).

that new safety information should be added to the label for its drug, it is directed to contact FDA with “adequate supporting information.” 57 Fed. Reg. at 17,961. The agency will consider this information and determine whether the labeling for both the generic drug and the innovator drug should be revised. *Id.*⁴

B. Regulatory History of Paroxetine Hydrochloride.

This litigation involves the drug paroxetine hydrochloride, which is the active ingredient of the brand-name drug Paxil. FDA approved GlaxoSmithKline’s new drug application for Paxil in 1992, and approved Apotex Corp.’s application to market a generic form of the drug in 2003. Paroxetine hydrochloride is in the class of drugs known as “selective serotonin reuptake

⁴ The plaintiff asserts that 21 C.F.R. § 314.70(c) empowers a generic drug manufacturer to add a new warning to the label for its drug without prior FDA approval. That regulatory provision, however — like the other provisions of Title 21, Part 314, Subpart B of the Code of Federal Regulations — applies to applications involving drug products for which a full application has been submitted, *i.e.*, innovator drug products. Drug manufacturers that submit abbreviated applications to market generic drugs are subject to the requirements set forth in Title 21, Part 314, Subpart C. Although Subpart C contains a provision requiring applicants to “comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application,” 21 C.F.R. § 317.97, that provision does not modify the requirement that the drug label for a generic drug must be the same as the label for the approved innovator drug (with limited exceptions not relevant here). Any ambiguity in the regulatory text has been clarified by FDA, which explained at the time of promulgation that the regulations do not authorize generic drug manufacturers to add new warnings to the approved labeling for the innovator drug. See 57 Fed. Reg. at 17,961, 17,953, 17,955.

inhibitors" (SSRIs), which are used to treat depression and other psychological disorders.

In order to evaluate the safety and efficacy of paroxetine hydrochloride and other SSRIs, and to ensure that warning statements in the labeling are accurate and not misleading, FDA must distinguish between events that result from use of the drug and those resulting from the underlying disease. Drawing that distinction is most difficult where, as in the case of depression treated with an SSRI, the adverse events in question — suicide and suicidality — are also a known consequence of the disease.

Since 1992, the FDA-approved label for Paxil (and, subsequently, generic forms of paroxetine hydrochloride approved for marketing) has reflected the risk of suicide in patients using the drug. The original approved label warned that "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs." The label recommended "[c]lose supervision of high-risk patients," and also indicated that prescriptions "should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose." FDA Approval Letter NDA 20-031/S029, Attachment 1, at 5, Addendum ("Add.") 1-3.⁵

⁵ This history of FDA's regulatory actions involving SSRIs is derived from
(continued...)

Prior to October 2003, however, FDA had repeatedly determined, based on its scientific analysis of then-available information, that there was not adequate evidence of an association between adult use of paroxetine hydrochloride or other SSRIs and suicide or suicidality.

In July 1991, the FDA denied a citizen petition seeking FDA withdrawal of approval for Prozac, based on FDA's conclusion that "[t]he data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." July 26, 1991, letter from FDA to S. Block, at 1, Add. 4.

In September 1991, FDA's Psychopharmacological Drugs Advisory Committee met and, after hearing testimony and reviewing relevant scientific studies, voted against any change to the labeling for Prozac to warn of a risk of suicide or suicidality, based on the conclusion that there was not credible evidence that antidepressant drugs or any particular class of antidepressant drugs "cause the emergence and/or intensification of suicidality and/or other violent behaviors." Psychopharmacological Drugs Advisory Committee, Sept. 20, 1991, Transcript at 302, 331-332, Add. 5, 6-8. The head of FDA's Psychopharmacology Unit

⁵(...continued)
public documents, which are available at FDA's web site (www.fda.gov). FDA attached a number of the documents in their entirety as an addendum to the district court amicus brief. For the convenience of this Court, FDA is also attaching selected documents and excerpts from documents as an addendum to this brief.

explained to the Advisory Committee at that meeting that FDA had decided that “suicidal ideation” and “violent behaviors” should be added to the section of adverse reactions on the drug labeling entitled “Post-Introduction Reports,” but should not be listed in the “Precautions” section of the labeling because of the agency’s “lack of confidence in a causal link between the taking of the drug and those behaviors.” Transcript, at 136-137, Add. 9-11.

In 1992 and 1997, FDA denied citizen petitions requesting that FDA revise the approved labeling for Prozac to include a warning of suicide or suicidal thought. *See* June 3, 1992, letter from FDA to I. Hellander, Add. 12; June 25, 1997, letter from FDA to R. Meysenburg, Add. 29. In its 1992 response, FDA explained that the “currently available, relevant evidence” was “not sufficient to reasonably conclude that the use of Prozac is possibly associated with suicidal ideation and behavior.” Add. 12. FDA reached the same conclusion in 1997, noting that, although the agency had received numerous drug experience reports concerning Prozac and suicidal ideation and suicidality, the agency had determined after careful consideration “that no labeling revisions were warranted” as of that date, and that then-current labeling for Prozac “appropriately reflect[ed] the level of concern about Prozac and suicidality.” Add. 30.

In 2002, FDA conducted a review of SSRIs, in order to evaluate the state of scientific knowledge regarding a connection between the use of SSRIs and

suicide. *See* Andrew D. Mosholder, *Mortality and Suicide Rates in Randomized Controlled Trials of Psychiatric Drugs: Update 2002*, Add. 31. Based on that review, the agency concluded that the scientific evidence did not show an association between the use of anti-depressants, including SSRIs, and suicide. *See* Mosholder presentation, at 35, Add. 32 (summarizing finding that “[t]here were no significant differences in suicide rates between active treatments and placebo”).

In May 2003, FDA received a report from GlaxoSmithKline suggesting that *pediatric* patients who used Paxil were at an increased risk for suicide and suicidality. Based on this report and FDA’s subsequent internal analysis, FDA subsequently issued a public health advisory in October 2003 for *pediatric* users of Paxil, explaining that preliminary data suggested an excess of reports for suicidality in pediatric patients with major depressive disorder. *See* www.fda.gov/cder/drug/advisory/mdd.htm. However, FDA declined to take any similar action with respect to adult users of the drug, and in June 2003 explicitly reaffirmed the agency’s conclusion that “[t]here is no evidence that Paxil is associated with an increased risk of suicidal thinking in adults.” *See* FDA Talk Paper, www.fda.gov/bbs/topics/ANSWERS/2003/ans01230.html.

On July 30, 2003, FDA approved Apotex’s application to market its generic form of paroxetine hydrochloride, concluding that “the drug is safe and effective for use as recommended in the submitted labeling.” *See* July 30, 2003, Letter from

Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, to Apotex Corp., ANDA 75-356 (available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist).

In February 2004, FDA convened an advisory committee meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, and, following that meeting, issued a public health advisory in March 2004 directing manufacturers of ten SSRIs, including Paxil, to include stronger warnings on drug labels about the need to monitor adult patients for signs of worsening depression or suicidality. *See* FDA Talk Paper, www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html; FDA Public Health Advisory, www.fda.gov/cder/drug/AntidepressantsPHAd.htm. Even as of that date, FDA emphasized that it had “not concluded that these drugs cause worsening depression or suicidality” in adult patients. FDA Public Health Advisory; *see also* FDA, Questions and Answers on Antidepressant Use in Children, Adolescents, and Adults, www.fda.gov/cder/drug/antidepressants/Q&A_antidepressants.htm.

In 2005, FDA launched a comprehensive scientific review of existing studies to determine whether there is an increased risk of suicide or suicidal behavior in adults treated with antidepressant drugs. *See* FDA Public Health

Advisory, <http://www.fda.gov/cder/drug/advisory/SSRI200507.htm>; FDA Talk Paper, July 1, 2005, www.fda.gov/bbs/topics/ANSWERS/2005/ANS01362.html. As part of that review, GlaxoSmithKline conducted a meta-analysis⁶ of studies on Paxil that disclosed a higher incidence of suicidal behavior in young adults treated with paroxetine compared with placebo. See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=448>. GlaxoSmithKline filed a supplemental submission with FDA in April 2006 and, after the 30-day waiting period expired and FDA did not reject the proposed labeling change, modified the label for Paxil to include a warning that “[y]oung adults, especially those with [major depressive disorder], may be at an increased risk of suicidal behavior when treated with” PAXIL. See Paxil label, available via link from http://www.gsk.com/products/prescription_medicines/us/paxil.htm.

C. Factual and Procedural History of Litigation.

Between October 6 and October 18, 2003, Lois Ann Colacicco was treated with paroxetine hydrochloride manufactured by Apotex. On October 28, 2003, at the age of 55, she committed suicide.

Ms. Colacicco’s husband sued Apotex, the manufacturer of the paroxetine hydrochloride taken by Ms. Colacicco, and GlaxoSmithKline, the manufacturer of

⁶ A meta-analysis is a comprehensive evaluation of the data contained in a number of studies.

brand-name Paxil. The plaintiff alleges in relevant part that the defendants failed warn of an increased risk of suicide or suicidality in adult users of their drugs. Mr. Colacicco also brought a variety of other state-law claims against the defendants.

The district court dismissed the plaintiff's failure-to-warn claim on federal preemption grounds. The court held that state tort liability would conflict with FDA's determination as of October 2003 that "associating use of paroxetine hydrochloride with suicidality would have constituted misbranding" because there was inadequate scientific evidence to support such a warning. Slip op., at 17. The court also noted that imposition of liability on Apotex, Inc., for failure to provide a different warning on the label for its generic drug would conflict with federal prohibitions on making such a change without prior FDA approval. Slip op., at 18. In reaching these conclusions, the court gave weight to FDA's views as set forth in its amicus brief on the potential conflict between state tort liability and the accomplishment of federal regulatory objectives, as well as FDA's interpretation of its own regulations. Slip op., at 18-20.

ARGUMENT

FEDERAL LAW PREEMPTS A STATE TORT CLAIM ARISING OUT OF DRUG MANUFACTURERS' ALLEGED FAILURE TO PROVIDE A WARNING THAT FDA DETERMINED WAS NOT SCIENTIFICALLY SUPPORTED

A. FDA's scientific judgment in October 2003, when paroxetine hydrochloride was prescribed to, and taken by, Ms. Colacicco, was that there was no reasonable evidence available at that time of an association between adult use of the drug and suicide or suicidality. To include on a drug's label a warning about a drug's effects, when FDA has specifically determined that such a warning is not based on reliable scientific evidence, would be "false or misleading," 21 U.S.C. §§ 352(a), (f), and would constitute unlawful misbranding. 21 U.S.C. § 331(a), (b), and (k).

In considering the agency's views on drug labeling, it is critical to understand that, where warnings are concerned, more is not always better. In setting standards for drug labeling, FDA seeks to encourage the optimal level of use in light of reasonable safety concerns, by requiring scientific evidence that establishes an association between a drug and a particular hazard before warning of that association on a drug's labeling. *See* 21 C.F.R. § 201.80(e). Under-use of a drug based on dissemination of unsubstantiated warnings may deprive patients of efficacious and possibly lifesaving treatment. Further, allowing unsubstantiated

warnings would likely reduce the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible. In order to make appropriate judgments about drug use, prescribers need a “careful and truthful representation of benefits and risks,” which does not “discourage appropriate use of a beneficial drug” through the inclusion of unsubstantiated risks. 71 Fed. Reg. 3922, 3935 (2006).

In this case, the label for paroxetine hydrochloride has since 1992 recognized the risk of suicide or suicidality in patients treated with the drug, alerting physicians to be aware of the “possibility of a suicide attempt” and to undertake “[c]lose supervision of high-risk patients.” The plaintiff asserts that the label for Paxil and its generic forms should have warned of an *increased* risk for suicide or suicidality in adults. But during the twelve-year period leading up to October 2003, FDA specifically considered and repeatedly rejected the addition of such a warning to the labeling for the drug. *See pp. 8-13, supra.* In responses to citizen petitions, in reviewing scientific studies and presenting its findings to advisory committees, and in its public statements, FDA concluded that the available scientific evidence did not support an association between adult SSRI use and suicide or suicidality.⁷

⁷ The plaintiff challenges the district court’s reliance on public documents
(continued...)

The plaintiff argues that the defendants could have warned of an increased risk of suicide or suicidality in adult users of paroxetine hydrochloride under federal regulations permitting a drug manufacturer to submit a supplemental application to add or strengthen a warning on a label, and to implement that change if the FDA does not object. *See* Br. 15 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). The regulation does not apply to the manufacturer of a generic drug. *See* pp. 7-8, *infra*. In addition, the regulation requires that even the manufacturer of an innovator drug must provide “a full explanation of the [scientific] basis for the change” sought to the labeling, 21 C.F.R. § 314.70(c)(3), (6)(iii), and does not alter the requirement that any warning must be based on “reasonable evidence of an association of a serious hazard with a drug.” 21 C.F.R. § 314.80(e). As of October 2003, any warning of an association between adult use of paroxetine hydrochloride and suicide or suicidality would have been misleading, because it would have been contrary to FDA’s determination that

⁷(...continued)
reflecting these decisions by FDA. *See* Br. 24-25 & n.9. A district court may take judicial notice of public records for the purpose of establishing the fact of an agency decision, rather than the truth of the underlying facts. *See, e.g., Lum v. Bank of Am.*, 361 F.3d 217, 221 n.3 (3d Cir.), cert. denied, 543 U.S. 918 (2004); *Pension Benefit Guar. Corp. v. White Consol. Indus., Inc.*, 998 F.2d 1192, 1197 (3d Cir.1993), cert. denied, 510 U.S. 1042 (1994). The plaintiff cannot reasonably claim that FDA did not take the actions reflected in public documents and referenced by the district court.

there was not adequate scientific evidence to establish such an association. Had the defendants added to their label the warning that the plaintiff seeks, they would have acted in violation of federal law. *See* 21 U.S.C. § 352(a), (f).

As the Supreme Court recognized in *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005), the imposition of a common-law duty through a state tort suit can be preempted under the Supremacy Clause if the duty at issue is inconsistent with the requirements of federal law.⁸ Here, Mr. Colacicco seeks to impose liability under state tort law for defendants' alleged failure to provide a warning that had been specifically rejected by FDA as of October 2003, and accordingly would have constituted unlawful misbranding had it been included on the labeling for the defendants' drugs.⁹ In such circumstances, the Supremacy Clause bars the

⁸ Amici curiae Jacquelyn Giles and Annabel Dobbs suggest (at Br. 3-4) that federal requirements do not preempt inconsistent state law unless they are carried out by FDA through means of a formal enforcement action. That puzzling suggestion — which would have sweeping consequences — is without precedential support. Cf. *Geier*, 529 U.S. at 882 (rejecting similar argument that state tort duty is not preempted because it does not impose mandatory requirement on liable party, who can pay judgment rather than modify its conduct).

⁹ Amici curiae Giles and Dobbs argue that FDA would not have rejected a proposed warning about an increased risk of adult suicide or suicidality, relying on congressional testimony by an FDA official about a drug manufacturer's change to the labeling for Effexor in August 2003 to add a warning relating to pediatric use of the drug. *See* Giles Br. 5-6. The fact that FDA had evidence suggesting an association between *pediatric* treatment with SSRIs and suicide or suicidality, *see* p. 12, *supra*, does not mean that reasonable scientific evidence suggested an

(continued...)

imposition of liability under state law. *See, e.g., Geier v. American Honda Motor Co.*, 529 U.S. 861, 881-882 (2000); *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1179 (5th Cir. 1988).

B. The plaintiff argues that federal preemption cannot apply because FDA did not affirmatively prohibit the defendants from adding a warning about suicide or suicidality to the labeling for their drugs. *See App. Br. 23-24 & n.8.* As the Supreme Court held in *Geier*, however, it is not necessary to have a “specific, formal agency statement identifying conflict” for federal preemption to apply. 529 U.S. at 884. Rather, state law is preempted if it would “stand[] as an obstacle to the accomplishment and execution” of the objectives of federal law. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

In the context of drug labeling, Congress has authorized FDA to apply its scientific expertise to determine, in the first instance, what warnings are appropriate and necessary for a particular drug. *See Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996); *Public Citizen Health Research Group v. Commissioner*, 740 F.2d 21, 28 (D.C. Cir. 1984). Given FDA’s repeated and specific determinations

⁹(...continued)
association between *adult* use of SSRIs and suicide or suicidality. FDA’s own actions leading up to and in October 2003, when the agency issued a public health advisory for pediatric users of Paxil but declined to warn adult users of the drug, foreclose the argument that FDA would have permitted the warning that the plaintiff seeks.

during the relevant time that it would be inappropriate to warn on the label for paroxetine hydrochloride of an association between adult use of the drug and suicide or suicidality, it would frustrate the regulatory scheme established by Congress to hold as a matter of state law that the defendants are liable for failing to provide that very warning on the label for their drugs.

The fact that FDA's judgment was not made in response to an application filed by the defendants does not preclude the application of federal preemption to the plaintiff's failure-to-warn claim in this litigation. A holding that FDA's labeling decision only has preemptive force if made in the course of rejecting a manufacturer's supplemental application for a labeling change would undermine FDA's regulatory authority, and would encourage manufacturers to file supplemental applications for unsubstantiated labeling changes, in order to shield themselves from tort liability.

In arguing that federal preemption does not apply, the plaintiff relies heavily on *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), but the regulatory scheme in that case explicitly provided that compliance with "minimum safety standards" imposed by the Coast Guard would "not relieve a person from liability at common law or under State law." *Id.* at 58-59 (emphasis added). Furthermore, and in accordance with its delegated authority under the statute, the Coast Guard had determined that federal preemption of state safety standards was limited to matters

covered by federal regulations. *See id.* at 60. After the Coast Guard declined to adopt a regulation requiring propeller guards on all motorboats, the Court properly held that this action did not bar a state tort liability for failure to install a guard on a particular motorboat — relying heavily on the Coast Guard’s view that the state claim would not conflict with federal regulatory objectives. *Id.* at 65-66.

Here, in sharp contrast, the imposition of liability under state law for defendants’ alleged failure to warn *would* interfere with FDA’s accomplishment of regulatory objectives. The Supreme Court explicitly recognized in *Sprietsma* that, where an agency’s decision not to impose a requirement in a particular setting reflects its judgment that the requirement would be inappropriate or unsound, the agency’s decision must be given preemptive effect. 537 U.S. at 66-67. Here, FDA’s repeated rejections of the proposed warning prior to October 2003 were based on its determinations that there was not adequate scientific evidence of an association between adult SSRI use and suicide or suicidality. Permitting a judge or jury to second-guess this judgment would interfere with FDA’s authority over drug labeling, and is barred by the Supremacy Clause. *See, e.g., Sprietsma*, 537 U.S. at 67-68; *Geier*, 529 U.S. at 884-885; *Jones v. Rath Packing Co.*, 430 U.S. 519, 543 (1977).¹⁰

¹⁰ In explaining that federal preemption bars the plaintiff’s failure-to-warn
(continued...)

C. The plaintiff's failure-to-warn claims against Apotex, the manufacturer of the generic form of paroxetine hydrochloride with which Ms. Colacicco was treated, are barred by federal preemption for an additional reason: under federal law, a generic drug manufacturer is prohibited from changing the label for its drug product without prior FDA approval.

By statute and regulation, generic drug labels are required to replicate the warnings contained in the approved labeling for the innovator, or name-brand,

¹⁰(...continued)

claim, FDA wishes to make clear that state tort liability is not preempted as a matter of law in every case in which liability is premised on a manufacturer's alleged common-law duty to provide a warning not yet required by FDA. Federal regulations explicitly recognize that manufacturers can, and in some limited instances must, modify their labels to add new warnings of hazards associated with the drug, without awaiting prior FDA approval. *See* 21 C.F.R. § 314.70(c)(7); 21 C.F.R. § 201.56. Where, in light of new scientific evidence or other changed circumstances, a drug label no longer ensures safe and effective use, FDA allows drug manufacturers to work quickly and collaboratively with the agency to make necessary labeling changes. Of course, even in these instances, FDA retains ultimate responsibility to determine whether the proposed change is appropriate, and may reject a labeling change and order the drug manufacturer to cease distributing the product with the new label. *See* 21 C.F.R. § 314.70(c)(5).

In order to determine whether the imposition of state tort liability on a drug manufacturer for failure to warn would conflict with FDA's regulatory authority or interfere with the accomplishment of federal objectives, therefore, a court must analyze the agency's public actions with regard to a particular drug as well as the common-law duty sought to be imposed. If the agency had made a determination at the relevant time that a particular warning was unsubstantiated or would otherwise render a drug misbranded, then federal preemption bars liability for the failure to provide that warning.

drug. *See* 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(2)(C); 21 C.F.R. § 314.150(b)(10).

Accordingly, a generic drug manufacturer may not modify the labeling for its drug product to add a new warning or caution. If a generic drug manufacturer “believes that new safety information” should be included on the product’s labeling, the manufacturer must “provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and [innovator] drugs should be revised.” 57 Fed. Reg. at 17,961. Without prior FDA approval, however, no such change can be made.

The plaintiff’s claim against Apotex is premised on the theory that Apotex had an obligation to modify its label under 21 C.F.R. § 314.70(c) to add a new warning for suicide or suicidality. As we have explained, however (at pp. 7-8, *supra*), that provision does not permit generic manufacturers to modify their drug labeling without FDA approval. *See* 57 Fed. Reg. 17,950, 17,961. Generic drug manufacturers are required both by statute and by regulation to use drug labeling that is the same in relevant respects “as the labeling approved for the listed drug.” 21 U.S.C. § 355(j)(2)(a)(v); *see also* 21 C.F.R. § 314.150(b)(10) (providing for FDA withdrawal of approval for generic drug application if the drug label is not identical to the label for the innovator drug).

In arguing that 21 C.F.R. § 314.70(c) permits generic drug manufacturers to make labeling changes without prior FDA approval, the plaintiff cites a recent

agency guidance document, *see* Br. 44, but that document explicitly provides that it is not “intended to expand the circumstances in which an applicant may effect labeling changes” under that provision, particularly “*those pertaining to generic drugs.*” <http://www.fda.gov/cder/guidance/7113dft.htm> (emphasis added). The agency’s construction of its governing statute and its own regulations not to permit labeling changes by generic drug manufacturers without prior FDA approval, which was set out with a full and cogent explanation at the time of FDA’s adoption of procedures for abbreviated new drug applications for generic drugs, was properly given deference by the district court.

D. In addition to challenging the substance of the district court’s holding that state tort liability for failure-to-warn would conflict with federal law, the plaintiff also challenges the general legal standards applied by the court. Specifically, the plaintiff argues that the court should not have based preemption on a federal regulation; and that the court gave undue deference to FDA’s view of the preemptive effect of labeling decisions relating to Paxil. *See* Br. 33-35, 41-47. As we next demonstrate, those contentions lack merit.

The plaintiffs’ argument that FDA’s labeling decisions cannot have preemptive effect because only Congress can displace state law, *see* App. Br. 11-12, is flatly inconsistent with *Fidelity Federal Savings & Loan Ass’n v. de la Cuesta*, 458 U.S. 141 (1982). There, the Supreme Court held that it was

“misdirected” for a court to focus narrowly “on Congress’ intent to supersede state law.” *Id.* at 154. The relevant question, the Court held, was whether the federal agency intended for its actions to preempt state law and, if so, whether those actions were within the scope of the agency’s delegated authority from Congress.

Id. Here, Congress has empowered the FDA to determine whether a particular warning is appropriate for the labeling of a prescription drug, and any state law that stands as an obstacle to this regulatory objective is accordingly preempted.

See, e.g., Geier, 529 U.S. 881-882.

Furthermore, it was wholly appropriate for the district court to give weight to FDA’s views on the applicability of implied conflict preemption in this case. Both the Supreme Court and this Court have recognized that a reviewing court should give weight to a federal agency’s views in determining whether imposition of liability under state law would interfere with the accomplishment of federal regulatory objectives. *See, e.g., Geier*, 529 U.S. at 883 (relying on agency amicus brief); *Horn v. Thoratec Corp.*, 376 F.3d 163, 171, 177-179 (3d Cir. 2004) (relying on FDA amicus brief). After all, Congress has delegated to the agency the authority to implement the statutory scheme, and the agency is “likely to have a thorough understanding of its own regulation and its objections and is uniquely qualified to comprehend the likely impact of state requirements.” *Geier*, 529 U.S. at 883 (quotation marks omitted).

Here, the agency has repeatedly explained that federal preemption bars the imposition of state tort liability for the failure to provide a warning for a drug product that conflicts with or is contrary to FDA-approved labeling. *See* 71 Fed. Reg. 3922, 3934 (rejecting suggestion that drug manufacturer has state-law duty to label products “with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated”). FDA has expressed similar views in amicus briefs dating back to at least 2000.¹¹ Furthermore, FDA rules adopted in 1979 reflect the agency’s views that the ultimate decision whether to require a warning on a drug label rests with FDA, and that federal law prohibits inclusion of statements on a label that FDA has determined not to be supported by substantial evidence. *See, e.g.*, 44 Fed. Reg. 37,434, 37,435, 37,441, 37,447 (1979). A

¹¹ *See, e.g., Kallas v. Pfizer, Inc.*, No. 2:04cv0998, Amicus Brief for United States (D. Utah. filed Sept. 15, 2005) (explaining that drug manufacturer may not be held liable for failure to warn of association between pediatric use of Zoloft or other SSRIs and suicide, where FDA had determined at relevant time that there was not reasonable evidence of such an association); *Motus v. Pfizer, Inc.*, No. 02-55498, Amicus Brief for United States (9th Cir. filed Sept. 3, 2002) (explaining that drug manufacturer may not be held liable for failure to warn of alleged danger where FDA had made contemporaneous determination that there is no scientific basis for such warning); *Bernhardt v. Pfizer, Inc.*, No. 00 Civ. 4042 (LMM), Statement of Interest of United States (S.D.N.Y. filed Nov. 13, 2000) (explaining that federal law preempts state claims seeking to require additional warnings on drug labels, and emphasizing that approval of drug labels is within primary jurisdiction of FDA).

fortiori, where state law seeks to impose a conflicting or contrary requirement, it must be preempted.

The plaintiff attempts to manufacture an inconsistency in the agency's views by pointing to a statement in a proposed rulemaking in 2000 that new guidelines for drug labels would not "have federalism implications or [] preempt State law." Br. 42 (quoting 65 Fed. Reg. 81,082, 81,103 (2000)). The plaintiff fails to understand, however, that the basis for federal preemption is not the guidelines themselves or the preamble to that proposed rulemaking, but rather FDA's repeated determinations prior to October 2003 that there was insufficient scientific evidence of an association between adult use of SSRI and suicide or suicidality to permit a warning on the labeling for those drugs — in tandem with statutory and regulatory requirements prohibiting the misbranding of drug products and barring generic drug manufacturers from modifying their labels without prior FDA approval.

The plaintiff also argues that FDA expressed a contrary view on preemption in a preamble to a 1998 agency rule, in which FDA explained that a regulation providing for agency approval of patient labeling of products was "not intended to preclude the states from imposing additional labeling requirements." 63 Fed. Reg. 66,378, 66,384 (1998). Nothing in that preamble — which explicitly recognized that state law cannot "alter" FDA-required labeling, *id.* — suggests that, where

FDA has rejected a specific warning as lacking an adequate scientific basis; that warning may nonetheless be required by operation of state law. In any event, even if FDA's position did mark a change in position, it would still be entitled to deferential consideration by this Court. *See, e.g., Horn*, 376 F.3d at 171; *Buckman v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-379, 354 n.2 (2001); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 714-715 (1985).

CONCLUSION

For the foregoing reasons, the Court should affirm the district court's dismissal on federal preemption grounds of the plaintiff's failure-to-warn claims.

Respectfully submitted,

DANIEL MERON
General Counsel
Department of Health and
Human Services

SHELDON T. BRADSHAW
Chief Counsel

ERIC M. BLUMBERG
Deputy Chief Counsel

JENNIFER E. CARUSO
Associate Chief Counsel
Food and Drug Division

Department of Health and
Human Services
Office of General Counsel

PETER D. KEISLER
Assistant Attorney General

C. FREDERICK BECKNER III
Deputy Assistant Attorney
General

PATRICK L. MEEHAN
United States Attorney

DOUGLAS N. LETTER
(202) 514-3602
/s/ Sharon Swingle
SHARON SWINGLE
(202) 353-2689
Attorneys, Appellate Staff
Department of Justice
Civil Division
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

DECEMBER 2006

**CERTIFICATE OF COMPLIANCE WITH
FEDERAL RULE OF APPELLATE PROCEDURE 32(a)**

I hereby certify that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 6,723 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the typestyle requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared with Word Perfect 12 in a proportional typeface with 14 characters per inch in Times New Roman.

/s/ Sharon Swingle
Sharon Swingle
Counsel for the United States

CERTIFICATE OF SERVICE AND ELECTRONIC FILING

I hereby certify that on December 4, 2006, I served the Court and the following counsel of record with an electronic copy of the Brief for Amicus Curiae the United States of America in PDF format. The electronic copy of the brief was scanned with Trend Micro OfficeScan and found to be virus-free. The text of the electronical copy of the brief is identical to the text of the hard copy of the brief. I also caused ten hard copies of the Brief for Amicus Curiae the United States of America to be served on the Court and two hard copies to be served on the following counsel by overnight delivery, postage prepaid:

Harris Pogust	Chilton D. Varner
Derek Braslow	Andrew T. Bayman
Cuneo, Pogust & Mason, LLP	Erica M. Long
161 Washington Street, Suite 1520	S. Samuel Griffin
Conshohocken, PA 19428	King & Spaulding
Charles A. Fitzpatrick, III	1180 Peachtree Street
Arthur B. Keppel	Atlanta, GA 30309
Mylotte, David & Fitzpatrick	Joseph K. Hetrick
Whetstone Run Office Complex	David J. Stanoch
450 Parkway, Suite 300	Joshua G. Schiller
Broomall, PA 19008	Dechert, LLP
	2929 Arch Street, 18th Street
	Philadelphia, PA 19104-2808

/s/ Sharon Swingle
Sharon Swingle
Counsel for the United States

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EXHIBIT I

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

JOSEPH C. COLACICCO,)
Individually and as Executor of the)
Estate of Lois Ann Colacicco, deceased,)
Plaintiff,)
v.) Civil Action No. 05-CV-05500-MMB
APOTEX, INC.; APOTEX CORP. as)
Subsidiary of Apotex, Inc.; and)
SMITHKLINE BEECHAM,)
doing business as GlaxoSmithKline,)
Defendants.)

BRIEF FOR *AMICUS CURIAE*
THE UNITED STATES OF AMERICA

Of Counsel:

PAULA M. STANNARD
Acting General Counsel
Department of Health and
Human Services

SHELDON BRADSHAW
Chief Counsel
ERIC M. BLUMBERG
Deputy Chief Counsel
JENNIFER E. CARUSO
Associate Chief Counsel
Food and Drug Division
Department of Health and
Human Services
Office of General Counsel

PETER D. KEISLER

Assistant Attorney General

JEFFREY BUCHOLTZ

Principal Deputy Assistant Attorney General

PATRICK L. MEEHAN

United States Attorney

VIRGINIA A. GIBSON

Assistant United States Attorney
Chief, Civil Division

DOUGLAS N. LETTER

(202) 514-3602

SHARON SWINGLE
(202) 353-2689
Attorneys, Appellate Staff
Department of Justice
Civil Division
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

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This brief is submitted pursuant to 28 U.S.C. § 517 and this Court's order of April 19, 2006.

The plaintiff in this litigation seeks to impose tort liability on drug manufacturers for failure to warn of an alleged danger, notwithstanding the Food and Drug Administration's (FDA's) repeated determination during the relevant period that there was not an adequate scientific basis for such a warning. The Court has requested FDA's views on preemption, including specifically the extent to which a court may consider agency views on preemption articulated in the course of a rulemaking that post-dates the conduct giving rise to this litigation. The Court has also inquired about the administrative law requirements, if any, applicable to agency views articulated in a preamble to a final rule.

Although FDA has the deepest sympathy for the plaintiff because of the loss of his wife, it is vital to ensure that state tort law does not undermine FDA's authority to protect the public health through enforcement of the prohibition against false or misleading labeling of drug products in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (FDCA). To base a tort judgment on drug manufacturers' failure to warn in October 2003 of an association between adult use of paroxetine hydrochloride and suicide or suicidality, despite FDA's judgment at that time that there was not reasonable evidence of such an association, would be to demand a warning statement that would have been false or misleading, and thus contrary to federal law. In such a case, federal law must prevail.

The preemption principles that require dismissal of the plaintiff's failure-to-warn claims are well-established, and have been recognized by FDA both in rulemaking and in other contexts, dating back long before the events giving rise to this litigation. As the Supreme Court has recognized, it is entirely appropriate for a court applying principles of federal preemption to

consider an agency's assessment of its regulatory interests and the extent to which state tort liability would conflict with those interests, even if — which is not the case here — the agency's views are set out after the operative events in question, mark a change in agency position, and are expressed in an amicus brief or other public statement that is not the product of notice-and-comment rulemaking. To the extent that the preamble to the final labeling rule promulgated in 2006 bears on this case, it is appropriately considered by the Court.

Nevertheless, in responding to this Court's inquiries regarding the operative effect of the preamble to the 2006 rule, FDA believes it important to emphasize that the basis for federal preemption in this litigation is not the preamble itself. The agency actions that are the basis for federal preemption in this litigation are FDA's repeated determinations between 1991 and 2003 that reasonable evidence did not support a warning on the label for paroxetine hydrochloride of an association between adult use of the drug and suicide or suicidality. As we next explain in greater detail, those labeling decisions should be given full force and effect under the Supremacy Clause.

STATUTORY AND REGULATORY BACKGROUND

A. FDA is the expert federal agency charged by Congress with regulating the manufacture, sale, and labeling of prescription drug products.¹ In particular, FDA has been charged by Congress with ensuring that drugs sold in the United States are safe and effective, 21

¹ FDA is a component of the United States Department of Health and Human Services (HHS). The Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (FDCA), vests regulatory and enforcement authority in the Secretary of Health and Human Services. The Secretary has delegated this authority to the Commissioner of FDA. FDA Staff Manual Guides, Vol. II, § 1410.10 (available at http://www.fda.gov/smg/1410_10.html).

U.S.C. § 355(d) and § 393(b)(2)(B), and that they are not misbranded, 21 U.S.C. §§ 331(a), (b), and (k), 352, and 321(n).

In order to obtain FDA approval to market a new innovator drug, a manufacturer must submit a New Drug Application. *See* 21 U.S.C. § 355(b). The manufacturer must provide “full reports of investigations which have been made to show whether or not such drug is safe for use and *** effective in use.” *Id.* § 355(b)(1)(A). The manufacturer must also provide “specimens of the labeling proposed to be used for such drug.” *Id.* § 355(b)(1)(A). The application will be denied if the manufacturer does not provide, *inter alia*, “adequate tests *** to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.” *Id.* § 355(d)(1).

Once an innovator drug has been approved for sale, a drug manufacturer may seek approval under the FDCA to market a generic drug. The approval process for a generic drug is abbreviated, and does not require the manufacturer to show independent evidence of efficacy or safety. Instead, the manufacturer must show that the generic drug generally has the same active ingredients as an approved drug and is bioequivalent to that drug. *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iv). The manufacturer must also show that the “labeling proposed for the [generic] drug is the same as the labeling approved for” the innovator drug. *Id.* § 355(j)(2)(A)(v). The only labeling changes permitted to be made are changes to reflect a different manufacturer or that the generic drug has “a different active ingredient” or a different “route of administration, dosage form, or strength” from the innovator drug. *See id.* § 355(j)(2)(A), (j)(2)(C).

Following FDA approval to market a drug, drug manufacturers are subject to continuing obligations under the FDCA. *See* 21 U.S.C. § 355(k); 21 C.F.R. § 314.80, 314.98. A manufacturer must keep a record of any “adverse event associated with the use of a drug in humans, whether or not considered drug related,” and must periodically report these adverse events to FDA. *See* 21 C.F.R. §§ 314.80(a), (c), 314.98(a). For adverse events that are “serious and unexpected,” the manufacturer is required to report the event to FDA within 15 days after learning about the event, and is also required to conduct an investigation of each event and to provide follow-up information to FDA. *See* 21 C.F.R. § 314.80(c)(1).

B. The preemption issue raised by the Court’s letter implicates the labeling provisions of the FDCA, as implemented by FDA. Under the FDCA, a drug is unlawfully misbranded when its labeling is false or misleading in any particular, or does not provide adequate directions for use or adequate warnings against any use dangerous to health. *See* 21 U.S.C. § 331(a), (b), and (k); *id.* § 352(a), (f), (j); *id.* § 321(n). A prescription drug satisfies FDA labeling requirements if the drug manufacturer gives physicians and pharmacists sufficient information, including indications for use and “any relevant hazards, contraindications, side-effects, and precautions,” to allow those medical professionals to “use the drug safely and for the purposes for which it is intended * * *.” 21 C.F.R. § 201.100(c)(1). Under federal law, therefore, the evaluation of a drug’s safety and effectiveness is inextricably linked with the drug labeling. *See also* 50 Fed. Reg. 7452, 7470 (1985) (“Drug labeling serves as the standard under which FDA determines whether a product is safe and effective.”).

FDA regulations set forth specific requirements for prescription drug labeling. *See* 21 C.F.R. Part 201, Subparts A, B, and G. Prescription drug labels must contain “a summary of the

essential scientific information needed for the safe and effective use of the drug," which includes indications for use as well as a description of "serious adverse reactions and potential safety hazards" associated with use of the drug. 21 C.F.R. §§ 201.56(a), 201.57(c), (e). The labeling regulations are designed to require warnings of all known risks based on reliable scientific evidence. *See* 21 C.F.R. § 201.56(c), 201.57(c), (e) (requiring as a condition of a warning that there be "reasonable evidence of an association of a serious hazard with a drug").

As noted above, applications for both innovator drugs and generic drugs must include copies of the proposed labeling. For innovator drugs, FDA considers evidence submitted by the applicant, as well as other relevant scientific information known to the agency, to determine whether the label is accurate, truthful, and adequate. FDA and drug manufacturers discuss in detail the proposed drug labeling, including the various warnings to be placed on the product. Based on the known scientific evidence, appropriate warnings are drafted that identify established risks while avoiding inadequately substantiated risks, mention of which could improperly deter use of the drug to the detriment of the very patients it is designed to benefit. When FDA approves a new drug application for an innovator drug, it also approves the precise final version of the drug labeling, including even the type size and font to be used by the manufacturer in that labeling.

For generic drugs, FDA confirms as a condition of approval that, with exceptions not applicable here, the labeling is the same as the labeling approved for the innovator drug for which the drug is a generic form. 21 U.S.C. § 355(j)(4)(G). As noted above, generic drug manufacturers are required to use labeling that is, for all relevant purposes here, identical to the approved labeling for the innovator drug.

After a drug has been approved, a manufacturer may not deviate from FDA-approved product labeling, except in limited circumstances set forth in FDA regulations. For the manufacturer of an innovator drug who wishes to add or strengthen a warning statement on the approved labeling, the manufacturer may provide FDA with a supplemental submission regarding the proposed labeling change, providing a full explanation of the basis for the proposed change. *See* 21 C.F.R. § 314.70(c)(1), (3), (6)(iii)(A).² If the FDA has not rejected the supplement within 30 days after its submission, the manufacturer may distribute the drug with the new proposed labeling — although FDA may choose to reject the proposed labeling change even after this date, and may also order the drug manufacturer to cease distributing the drug with the new labeling. *See* 21 C.F.R. § 314.70(c)(7).

For a generic drug manufacturer, there is no statutory or regulatory provision permitting the manufacturer to make a labeling change to its generic drug without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. *See* 21 C.F.R. § 314.150(b)(10); *see also* 57 Fed. Reg. 17,950, 17,961 (1992). If a generic drug manufacturer believes that new safety information should be added to the label for the drug, the manufacturer must contact FDA with “adequate supporting information.” 57 Fed. Reg. at 17,961. The FDA will consider this information and will make a determination whether the labeling for both the generic drug *and* the innovator drug should be revised. *Id.*

C. This litigation involves the drug paroxetine hydrochloride, which is the active ingredient of the brand-name drug Paxil. FDA approved GlaxoSmithKline’s new drug

² Indeed, if the drug manufacturer has “reasonable evidence of an association of a serious hazard with a drug,” the manufacturer has an obligation to seek FDA approval for a labeling change, in order to add a warning of the new potential hazard. *See* 21 C.F.R. § 201.57(e).

application for Paxil in 1992, and the drug is currently approved to be marketed for use in treating major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. Apotex Corp. received approval in 2003 to market its generic form of paroxetine hydrochloride. Paroxetine hydrochloride is in the class of drugs known as "selective serotonin reuptake inhibitors" (SSRIs), which are used to treat depression and other psychological disorders.

In order to evaluate the safety and efficacy of paroxetine hydrochloride and other SSRIs in treating depression, and to ensure that warning statements in the labeling are accurate and not misleading, FDA must distinguish between events that result from use of the drug and those resulting from the underlying disease. Drawing that distinction is most difficult where, as in the case of depression treated with an SSRI, the adverse events in question — suicide and suicidality — are also a known consequence of the treated disease.

Since 1992, the FDA-approved label for Paxil (and, subsequently, generic forms of paroxetine hydrochloride approved for marketing) has reflected the risk of suicide in patients using the drug. The original approved label warned that "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs." The label recommended "[c]lose supervision of high-risk patients" in addition to drug therapy, and also indicated that prescriptions for Paxil "should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose." Attachment to FDA Approval Letter, NDA 20-031/S029, at 12.

Prior to October 2003, however, FDA had repeatedly determined, based on its scientific analysis of available information, that there was inadequate evidence of an association between

use of Paxil or other SSRIs by adult patients and a risk of suicide or suicidality to support a specific warning in the "Precautions" section of the drug's labeling.

In July 1991, the FDA denied a citizen petition seeking FDA withdrawal of approval for Prozac, based on FDA's conclusion that "[t]he data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." July 26, 1991, letter from FDA to S. Block, at 1 (copy attached at Exhibit A).

In September 1991, FDA's Psychopharmacological Drugs Advisory Committee met and, after hearing more than four hours of testimony and reviewing and discussing relevant scientific studies, voted unanimously that there was no "credible evidence to support a conclusion the antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors," and no evidence "to indicate that a particular drug or drug class poses a greater risk [than other anti-depressant drugs] for the emergence and/or intensification of suicidal thoughts and acts and/or violent behaviors." Dep't of Health and Human Servs., Public Health Service, Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, Sept. 20, 1991, Transcript at 302 (copy attached as Exhibit B). The Committee voted against any labeling change to warn against the risk of suicide or suicidality as a result of Prozac use.

See id. at 331-332.³

³ The head of FDA's Psychopharmacology Unit explained to the Advisory Committee at the 1991 meeting that FDA had received reports of adverse events regarding users of Prozac, and had determined that the terms "suicidal ideation" and "violent behaviors" should be added to the subsection of adverse reactions entitled "Post-Introduction Reports." FDA had explicitly decided at that time that the terms should not be listed in the "Precautions" section of the labeling, however, because of the agency's "lack of confidence in a causal link between the taking of the drug and those behaviors." Exh. B., at 136-137.

In 1992 and 1997, FDA denied citizen petitions requesting that FDA revise the approved labeling for Prozac to include a warning of suicide or suicidal thought. See June 3, 1992, letter from FDA to I. Hellander (copy attached as Exhibit C); June 25, 2997, letter from FDA to R. Meyenburg (copy attached as Exhibit D). In its 1992 response, FDA explained that the "currently available, relevant evidence" was "not sufficient to reasonably conclude that the use of Prozac is possibly associated with suicidal ideation and behavior." Exh. C, at 1. FDA detailed the available scientific studies and case reports, and concluded that they did "not permit a conclusion that Prozac, as opposed to the conditions for which Prozac was administered," was responsible for suicidal thought. Exh. C, at 3. As FDA noted, its own advisory committee had recently concluded "that the evidence was not strong enough to justify the suggestion of even the possibility of a causal linkage in the labeling." Exh. C, at 15. FDA reached the same conclusion in 1997, noting that, although the agency had received numerous drug experience reports concerning Prozac and suicidal ideation and suicidality, the agency had determined after careful consideration "that no labeling revisions were warranted" as of that date, and that then-current labeling for Prozac "appropriately reflect[ed] the level of concern about Prozac and suicidality" Exh. D, at 2.

In 2002, FDA conducted a review of SSRIs, in order to evaluate the current state of scientific knowledge regarding a connection between the use of SSRIs and suicide. See Andrew D. Mosholder, Medical Officer, FDA Division of Neuropharmacological Drug Products, *Mortality and Suicide Rates in Randomized Controlled Trials of Psychiatric Drugs: Update 2002*, 42nd Annual National Institute of Mental Health's New Clinical Drug Evaluation Unit Meeting (June 10-13, 2002) (copy of slide presentation attached as Exhibit E). After reviewing

studies involving randomized controlled trials of psychiatric drugs, the agency concluded that the scientific evidence did not show an association between the use of anti-depressants, including SSRIs, and suicide. *See* Exh. E, at 35 (summarizing agency's finding that "[t]here were no significant differences in suicide rates between active treatments and placebo" for patients with major depressive disorder, schizophrenia, or dementia).

In May 2003, FDA received a report from GlaxoSmithKline suggesting that *pediatric* patients who used Paxil were at an increased risk for suicide and suicidality. Based on this report and FDA's subsequent internal analysis, FDA issued a public health advisory in October 2003 for *pediatric* users of Paxil, explaining that preliminary data suggested an excess of reports for suicidality in pediatric patients with major depressive disorder. *See* www.fda.gov/cder/drug/advisory/mdd.htm. However, FDA declined to warn of any similar risk for *adult* patients at that time, merely emphasizing that — as already indicated by the labeling for Paxil and Apotex's generic form of paroxetine hydrochloride — all patients treated with antidepressant drugs for major depressive disorder face a risk of suicide and should be closely supervised. *See id.*; FDA Talk Paper, T03-70, Oct. 27, 2003, www.fda.gov/bbs/topics/ANSWERS/2003/ans01256.html.

In March 2004, for the first time, FDA issued a public health advisory directing manufacturers of ten SSRIs, including Paxil, to include stronger cautions and warnings on drug labels about the need to monitor adult patients for signs of worsening depression or suicidality. *See* FDA Talk Paper, www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html; FDA Public Health Advisory, www.fda.gov/cder/drug/AntidepressantPHA.htm. Even as of that date, FDA emphasized that it had "not concluded that these drugs cause worsening depression or suicidality" in adult patients, or that certain symptoms associated with antidepressant use in

some adult patients — including agitation and akathisia (severe restlessness) — were a precursor to worsening depression or suicidality. FDA Public Health Advisory; *see also* FDA, Questions and Answers on Antidepressant Use in Children, Adolescents, and Adults, www.fda.gov/cder/drug/antidepressants/Q&A_antidepressants.htm. Currently, FDA is engaged in a comprehensive scientific review of existing studies, involving hundreds of clinical trials and thousands of adult patients, to determine whether there is an increased risk of suicide or suicidal behavior in adults treated with antidepressant drugs. *See* FDA Public Health Advisory, www.fda.gov/cder/drug/advisory/WWRI200507.htm; *see also* FDA Talk Paper, July 1, 2005, www.fda.gov/bbs/topics/ANSWERS/2005/ANS01362.html.⁴

D. Between October 6 and October 18, 2003, Lois Ann Colacicco was treated with paroxetine hydrochloride manufactured by Apotex. On October 28, 2003, at the age of 55, she committed suicide.

Ms. Colacicco's husband brought this lawsuit in federal court under state law against Apotex, the manufacturer of the paroxetine hydrochloride taken by Ms. Colacicco, and GlaxoSmithKline, the manufacturer of the brand-name drug. Mr. Colacicco alleges that his wife was inadequately informed of the adverse effects of the drug, and specifically that Apotex and/or GlaxoSmithKline failed to provide adequate warnings to potential users that the drug could

⁴ On May 8, 2006, GlaxoSmithKline announced that, based on a meta-analysis of studies of Paxil that the company completed in 2006, GlaxoSmithKline had discovered a higher incidence of suicidal behavior in adult patients with major depressive disorder treated with paroxetine compared with placebo, as well as a higher incidence of suicidal behavior in young adults treated with paroxetine compared with placebo. *See* http://www.gsk.com/media/paroxetine_adult.htm. GlaxoSmithKline has filed a supplemental submission with FDA seeking approval for a new warning on the label for Paxil that "young adults, particularly those with depression, may be at an increased risk of suicidal behavior (including suicide attempts) when treated with PAXIL."

cause suicidality, violence, and aggression. Mr. Colacicco also alleges that Apotex and/or GlaxoSmithKline failed to adequately inform FDA, physicians, and potential users that Paxil is not effective to treat depression in some adult users, and causes an increased risk of suicide and suicidality in some adults. In addition to alleging that the defendants are liable for failure to provide adequate warnings, Mr. Colacicco seeks to impose liability for breach of warranty, fraud, negligent misrepresentation, intentional and negligent infliction of emotional distress, negligence, negligence *per se*, strict product liability, wrongful death, and violation of state consumer protection laws.⁵

The defendants sought dismissal on numerous grounds, including federal preemption. Following briefing by the parties on the defendants' motions to dismiss, the district court directed the parties and, subsequently, FDA, to provide views regarding the applicability in this litigation of the preamble to FDA's recent rule on drug labeling, 71 Fed. Reg. 3922 (2006), the validity of the preamble as a rule of decision, and whether it would be impermissibly retroactive to apply the policy set out in the preamble to claims arising out of conduct that predated the preamble's issuance. On May 4, 2006, the Court sent FDA an additional letter, asking for details regarding any potential change in agency position regarding preemption, as well as opportunities for public comment on the agency's position.

⁵ At this early stage of the proceedings, and in light of the plaintiff's primary reliance on the theory that defendants are liable for failure to include a warning on their drug labeling in October 2003 of an asserted association between paroxetine hydrochloride and adult suicide or suicidality, FDA has focused on that failure-to-warn theory in its discussion of federal preemption. The agency takes no position on the viability of the plaintiff's other claims, or the potential applicability of federal preemption to those claims.

ARGUMENT

L. FEDERAL LAW PREEMPTS A STATE TORT CLAIM ARISING OUT OF DRUG MANUFACTURERS' ALLEGED FAILURE TO PROVIDE A WARNING THAT FDA HAD DETERMINED WAS NOT SCIENTIFICALLY SUPPORTED.

A. FDA's scientific judgment in October 2003, when paroxetine hydrochloride was prescribed to, and taken by, Ms. Colacicco, was that there was no reasonable evidence available at that time of an association between adult use of the drug and suicide or suicidality. To include on a drug's label a warning about a drug's effects, when FDA has determined that such a warning is not based on reliable scientific evidence, would be "false or misleading," 21 U.S.C. §§ 352(a), (f), and would constitute unlawful misbranding. 21 U.S.C. § 331(a), (b), and (k). Under the Supremacy Clause (U.S. Const. art. VI, cl. 2), a state may not cause a drug manufacturer to choose between compliance with federal law and state tort liability. *See Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000) (Supremacy Clause forbids "'conflicts' that make it 'impossible' for private parties to comply with both state and federal law"). Necessarily, therefore, federal conflict preemption bars Mr. Colacicco's attempt to impose liability under state tort law for defendants' alleged failure to provide a warning for Paxil or its generic equivalent that would have violated federal drug labeling provisions.

In considering the agency's views on drug labeling, it is critical to understand that, where warnings are concerned, more is not always better. FDA's requirement that a warning must be scientifically substantiated is designed to ensure each drug's optimal use. Under-use of a drug based on dissemination of unsubstantiated warnings would deprive patients of efficacious, possibly lifesaving treatment, thereby undermining the benefits of federal regulation. Further, allowing unsubstantiated warnings would likely diminish the impact of valid warnings by

creating an unnecessary distraction and making even valid warnings less credible. In this respect, the plaintiff's assertion that "[f]ederal prescription drug labeling regulations are merely 'minimum standards,'" Docket No. 17-3, is erroneous.

Rather than set minimum standards for warnings in drug labeling, FDA seeks to encourage the optimal level of use in light of reasonable safety concerns, by requiring scientific evidence of an association between a drug and a particular hazard before warning of that association on a drug's labeling. *See* 21 C.F.R. § 201.57(e). Notably, the plaintiff does not argue that the label for paroxetine hydrochloride failed to make physicians aware of the possible risk of suicide or suicidality in patients treated with the drug. From 1992 onward, the label explicitly warned about the "possibility of a suicide attempt," and cautioned treating physicians to undertake "[c]lose supervision of high-risk patients."

The plaintiff nonetheless asserts that manufacturers of Paxil or its generic equivalent should have warned of an "increased risk" of suicide or suicidality in adults taking Paxil and other SSRIs. *See, e.g.*, Complaint ¶¶ 28-29, 34, 50, 68. During the relevant period for purposes of this litigation, however, FDA had specifically and repeatedly rejected claims that adult use of SSRIs was associated with an increased risk of suicide or suicidality. *See* pp. 7-10, *supra*. In responses to citizen petitions, in its internal review of scientific studies, and in its advisory committee meetings, FDA repeatedly concluded that the available scientific evidence did not support an association between adult SSRI use and suicide. FDA specifically rejected, during this time period, proposed warnings of such an association.

Under these circumstances, and in light of the agency's judgment as of October 2003 that there was not reasonable evidence of an association between adult use of paroxetine chloride and

suicide or suicidality, any warning of such an association would have been barred as a matter of federal law. Although FDA regulations permit a "pioneer" new drug manufacturer to submit a supplement to add or strengthen a warning on a label, and to carry out that change without waiting for prior FDA approval, the regulations also require the innovator manufacturer to provide "a full explanation of the [scientific] basis for the change," and do not alter the statutory requirement that a manufacturer may not misbrand a drug. *See* 21 C.F.R. § 314.70(c)(3), (6)(iii); 21 U.S.C. § 331(a), (b), and (k). As of October 2003, any warning of an association between adult use of paroxetine hydrochloride and suicide or suicidality would have been deemed "misleading" and, thus, a violation of federal law. *See* 21 U.S.C. § 352(a), (f). Accordingly, the Supremacy Clause precludes the imposition of liability under state law for the failure to provide such warning. *See, e.g., Hurley v. Lederle Labs.*, 863 F.2d 1173, 1179 (5th Cir. 1988); *see also Geier*, 529 U.S. at 881-882.⁶

B. The plaintiff suggests that state tort liability for failure to warn is permissible unless FDA has explicitly prohibited a manufacturer from warning about suicidality or aggression on the label for paroxetine hydrochloride. As the Supreme Court held in *Geier*, however, there is no requirement of "a specific, formal agency statement identifying conflict" for preemption to apply. 529 U.S. at 884. Rather, the operative question is whether a tort suit would "stand[] as an obstacle to the accomplishment and execution" of the objectives of federal law. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

⁶ As explained in further detail below, furthermore, submitting a supplement application and changing the drug labeling prior to FDA approval was not an available option to a generic drug manufacturer such as Apotex. *See* pages 16-17, *infra*.

In the context of drug labeling, Congress has authorized FDA to apply its scientific expertise to determine, in the first instance, what warnings are appropriate and necessary for a particular drug. See *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996); *Public Citizen Health Research Group v. Commissioner*, 740 F.2d 21, 28 (D.C. Cir. 1984). Given FDA's repeated determinations during the relevant time that it would be inappropriate to warn of an association between adult use of paroxetine hydrochloride and suicide or suicidality, it would stymie the regulatory scheme established by Congress to hold as a matter of state law that the defendants are liable for failing to provide such an inappropriate warning.⁷ Judicial imposition of liability for failure to warn would interfere with FDA's ability to protect the public from unsubstantiated warnings that would deter appropriate uses of a drug and diminish the impact of valid warnings. Even if compliance with both state and federal law in such an instance would not be impossible, state tort liability would pose a sufficient threat to federal regulatory objectives to support preemption under the Supremacy Clause. See, e.g., *Geier*, 529 U.S. at 884-885; *Jones v. Rath Packing Co.*, 430 U.S. 519, 543 (1977).

C. The plaintiff's failure-to-warn claims against Apotex Corporation and its parent company, Apotex, Inc. (collectively, Apotex), are preempted for the additional reason that the claims seek to impose liability on Apotex for its alleged failure to provide a warning that, as a generic drug manufacturer, Apotex was barred from giving without prior FDA approval.

⁷ In determining the proper role for state law in this context, furthermore, it is significant that the federal government has been regulating the manufacture and sale of drugs since 1906. As the Supreme Court recognized in *United States v. Locke*, 529 U.S. 89 (2000), any presumption against federal preemption "is not triggered when the State regulates in an area where there has been a history of significant federal presence." *Id.* at 108.

The plaintiff claims that Apotex had a duty to modify the label for paroxetine hydrochloride to add a warning regarding a risk of suicide. *See, e.g.*, Complaint ¶¶ 50, 86, 102(c). Elaborating on this legal theory in his response to Apotex's motion to dismiss, the plaintiff argues that Apotex should have filed a supplement to its application under 21 C.F.R. § 314.70(c), which allegedly would have permitted Apotex to provide the warning that the plaintiff claims should have been given.

Under federal law, however, generic drug labels are required to replicate the warnings contained in the approved labeling for the innovator, or name-brand, drug. *See* 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(2)(C); 21 C.F.R. § 314.150(b)(10). Accordingly, a generic drug manufacturer is not permitted to add a warning or caution to the label without prior approval from FDA. If a generic drug manufacturer "believes that new safety information should be added" to the product's labeling, the manufacturer must "provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and [innovator] drugs should be revised." 57 Fed. Reg. at 17,961. Only if the FDA directs that the labels for *both* the generic and the innovator drugs should be changed, can the generic drug manufacturer add a new warning or caution to the labeling for its drug.

For the reasons we have already explained, if Apotex had approached FDA in or prior to October 2003 to seek approval for a warning regarding suicide or suicidality on the label for paroxetine hydrochloride, FDA would have rejected the warning as scientifically unsupported. For this reason, as well, the failure-to-warn claims against Apotex are preempted by federal law.

II. FDA'S VIEWS ON PREEMPTION ARE PROPERLY CONSIDERED BY THIS COURT.

A. As we have explained, principles of conflict preemption bar the plaintiff's attempt to impose state tort liability on defendants for the asserted failure to provide a drug label warning in October 2003 that had been rejected as unsupported by FDA during the period in question. The same preemption principles are recognized in the preamble to the final rule adopted by FDA in January 2006. See 71 Fed. Reg. 3922, 3934 (noting that federal law preempts state-law labeling requirement that conflicts with or is contrary to FDA-approved labeling, and criticizing litigant's claim that a drug manufacturer has a state-law duty to label products "with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated").

As we have explained, the 2006 preamble is not itself the basis for federal preemption, which is triggered by FDA's repeated determinations prior to October 2003 that there was insufficient scientific evidence of an association between adult use of SSRI and suicide or suicidality to permit a warning on the labeling for those drugs. The plaintiff has not argued that FDA's labeling decisions were outside the scope of its statutory authority. Under these circumstances, implied conflict preemption bars state tort liability for failure to provide a warning as of October 2003 that had been rejected by FDA, regardless whether FDA explicitly claimed that its labeling decisions would have preemptive effect.

Nevertheless, the 2006 preamble sets out FDA's current understanding of the way in which a state tort judgment can interfere with FDA's implementation of federal law, and thus is properly considered by this Court. In proposing a new rule governing the format and content of drug labeling — a rule that did not itself explicitly preempt state law — FDA received comments about the product liability implications of the proposed rule. The Administrative Procedure Act

requires FDA to address the comments it receives, and FDA did so by explaining its view of the law of implied conflict preemption.⁸

Although the plaintiff has suggested that any argument for federal preemption of his failure-to-warn claims would constitute a wholesale change in agency position, in fact FDA has filed briefs dating back to at least 2000 taking the position that the Supremacy Clause bars state tort liability for failure to include a warning on a drug label that is in conflict with or contrary to the warnings approved by FDA. *See, e.g., Kallas v. Pfizer, Inc.*, No. 2:04cv0998 (D. Utah. filed Sept. 15, 2005) (explaining that drug manufacturer may not be held liable for failure to warn of association between pediatric use of Zoloft or other SSRIs and suicide, where FDA had determined at relevant time that there was not reasonable evidence of such an association); *Motus v. Pfizer, Inc.*, No. 02-55498, Amicus Brief for United States (9th Cir. filed Sept. 3, 2002) (explaining that drug manufacturer may not be held liable for failure to warn of alleged danger where FDA had made contemporaneous determination that there is no scientific basis for such warning); *Bernhardt v. Pfizer, Inc.*, No. 00 Civ. 4042 (LMM), Statement of Interest of United States (S.D.N.Y. filed Nov. 13, 2000) (explaining that federal law preempts state claims seeking to require additional warnings on drug labels, and emphasizing that approval of drug labels is within primary jurisdiction of FDA).

⁸ Neither the Administrative Procedure Act nor Executive Order 13,132 requires FDA to provide notice of and an opportunity to comment on responses to public comments about a proposed rule, setting forth the agency's view of principles of implied conflict preemption in a preamble that is not part of the codified final rule. Nevertheless, in adopting the final rule in 2006, FDA did consult with a number of organizations representing the interests of state and local governments about the potential interaction between FDA drug labeling requirements and state law. *See* 71 Fed. Reg. 3922, 3969 (2006).

Furthermore, FDA rules dating back to at least 1979 reflect the agency's views that the ultimate decision whether to require a warning on a drug label rests with FDA, and that federal law prohibits inclusion of statements on a label that FDA has determined not to be supported by substantial evidence. *See, e.g.*, 44 Fed. Reg. 37,434, 37,435, 37,441, 37,447 (1979). A fortiori, where state law seeks to impose a conflicting or contrary requirement, it must be preempted.

The Court inquired about the significance of a 1998 preamble to a final rule, in which FDA explained that a regulation providing for FDA approval of patient labeling for a limited number of products was "not intended to preclude the states from imposing additional labeling requirements." 63 Fed. Reg. 66,378, 66,384 (1998). However, nothing in that preamble suggests that where, as here, FDA has rejected a warning proposed for a drug's labeling as lacking an adequate scientific basis, that warning may nonetheless be required by operation of state law. To the contrary, the 1998 preamble explicitly recognized that state law cannot "alter" FDA-required labeling. *Id.* To the limited extent that the 1998 preamble might be relevant to this litigation, therefore, it supports application of federal preemption to the plaintiff's failure-to-warn claims in this litigation.⁹

B. The Supreme Court has repeatedly recognized that, in determining whether federal preemption bars a state-law claim, it is appropriate to consider a federal agency's views regarding conflict — even if those views are expressed for the first time in the course of litigation or otherwise post-date the events giving rise to the claim. The Supreme Court has also

⁹ Similarly, although the 2006 letter from three individual Members of Congress to FDA, appended to the plaintiff's March 27, 2006, letter to the Court, asserts that FDA has recently changed its position on preemption, that letter explicitly acknowledges that, under FDA's pre-2006 approach, federal law was considered to preempt conflicting state-law requirements. *See* Doc. 38, Exh. A-3.

held that the agency is not required to set out its views in a rule adopted after notice-and-comment rulemaking in order for those views to be given weight in the preemption analysis.

In *Geier*, for example, the Court explicitly relied on the Department of Transportation's explanation in an amicus brief regarding the agency's regulatory objectives, and the agency's conclusion that state tort liability would interfere with the accomplishment of those objectives, in holding that state-law claims were barred by federal preemption. 529 U.S. at 883. As the Supreme Court emphasized, Congress had delegated to the agency the authority to implement the statutory scheme in a complex and technical area, and the agency was "likely to have a thorough understanding of its own regulation and its objections and [to be] 'uniquely qualified' to comprehend the likely impact of state requirements." *Id.* at 883 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 496 (1996)).¹⁰ Obviously, the amicus brief filed by the Department of Transportation in *Geier* post-dated the events claimed to give rise to liability. *See also Horn v. Thoratec Corp.*, 376 F.3d 163, 171, 176-177 & n.22 (3d Cir. 2004) (relying on views set out in FDA's amicus brief to hold that failure-to-warn claims regarding medical device are preempted).

Similarly, in *Fidelity Federal Savings & Loan Ass'n v. de la Cuesta*, 458 U.S. 141 (1982), the Court relied in part on an agency rule post-dating the events in question to conclude

¹⁰ The *Geier* Court noted that the agency's description of its regulatory objectives and the potential interference with those objectives posed by application of state law had been consistent over time. 529 U.S. at 883. The same is true, as we have explained, of FDA's view regarding federal preemption of state tort claims seeking to impose liability for failure to give a warning specifically considered and rejected by the agency. In any event, the fact that an agency's view on conflict preemption marks a change from an earlier position does not preclude a court's consideration of, and deference to, the agency's assertion that state-law liability would interfere with the accomplishment of federal regulatory objectives. *See Buckman v. Plaintiffs' Legal Committee*, 531 U.S. 341, 347-349, 354 n.2 (2001); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 714-715 (1985); *Horn v. Thoratec Corp.*, 376 F.3d 163, 171 (3d Cir. 2004).

that state-law liability would interfere with the objectives of the federal regulatory scheme. *Id.* at 155-156. Indeed, in *Hillsborough County v. Automated Medical Laboratories, Inc.*, 471 U.S. 707 (1985), the Supreme Court suggested that federal preemption would apply despite an agency's explicit statement at the time it promulgated regulations that the regulations were not intended to have preemptive effect, if the agency subsequently changed its view on the strength of its interests in preemption or the effect of the regulations in question. *Id.* at 715, 721-722 & n.5.

The Supreme Court has also made clear that, in discussing the extent to which state law will interfere with federal regulatory objectives, an agency is not required to undertake notice-and-comment rulemaking for its views to be given weight by the Court. In *Geier*, the Court explicitly rejected such an argument, pointing out that requiring an agency to set out an explicit finding of conflict through formal rulemaking would permit "conflicts that an agency, and therefore Congress, is most unlikely to have intended." *Geier*, 529 U.S. at 885. In *Hillsborough County*, the Court recognized that an agency could express its views on preemption through a variety of sources, including "preambles" and "responses to comments." 471 U.S. at 718. Accordingly, to the extent that the 2006 preamble sheds additional light on FDA's view of the interference with the accomplishment of federal regulatory objectives that would result from state liability for failure to provide a warning rejected by the agency, the preamble is appropriately considered by this Court.

CONCLUSION

For the foregoing reasons, the Court should hold that the Supremacy Clause bars a state tort claim premised on defendants' failure to provide a warning in October 2003 of an association between adult use of paroxetine hydrochloride and suicide or suicidality.

Respectfully submitted,

Of Counsel:

PAULA M. STANNARD
Acting General Counsel
Department of Health and
Human Services

SHELDON BRADSHAW
Chief Counsel
ERIC M. BLUMBERG
Deputy Chief Counsel
JENNIFER E. CARUSO
Associate Chief Counsel
Food and Drug Division
Department of Health and
Human Services
Office of General Counsel

PETER D. KEISLER
Assistant Attorney General

JEFFREY BUCHOLTZ
Principal Deputy Assistant Attorney General

PATRICK L. MEEHAN
United States Attorney

VIRGINIA A. GIBSON
Assistant United States Attorney
Chief, Civil Division

DOUGLAS N. LETTER
(202) 514-3602
SHARON SWINGLE
(202) 353-2689
Attorneys, Appellate Staff
Department of Justice
Civil Division
950 Pennsylvania Ave., N.W.
Washington, DC 20530-0001

CERTIFICATE OF SERVICE

I hereby certify that on May 10, 2006, I caused two copies of the foregoing Brief for Amicus Curiae the United States of America and the accompanying Addendum to be served on the following counsel by overnight delivery, postage prepaid:

Derek Braslow
Cuneo, Pogust & Mason, LLP
Eight Tower Bridge
161 Washington Street, Suite 1520
Conshohocken, PA 19428

Arthur Keppel
Mylotte, David & Fitzpatrick
Whetstone Run Office Complex
450 Parkway, Suite 300
Broomall, PA 19008

David Stanoch
Dechert, LLP
2929 Arch Street
Philadelphia, PA 19104-2808

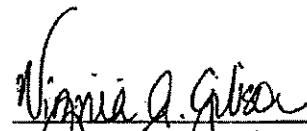

VIRGINIA A. GIBSON
Chief, Civil Division
Assistant United States Attorney

EXHIBIT J

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Parts 201, 314, and 601**

[Docket No. 2000N-1269] (formerly Docket No. 00N-1269)

RIN 0910-AA94

Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format of labeling for human prescription drug products (including biological products that are regulated as drugs). The final rule revises current regulations to require that the labeling of new and recently approved products include highlights of prescribing information and a table of contents. The final rule also reorders certain sections, requires minor content changes, and sets minimum graphical requirements. These revisions will make it easier for health care practitioners to access, read, and use information in prescription drug labeling. The revisions will enhance the safe and effective use of prescription drug products and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information. For both new and recently approved products and older products, the final rule requires that all FDA-approved patient labeling be reprinted with or accompany the labeling. The final rule also revises current regulations for prescription drug labeling of older products by clarifying certain requirements. These changes will make the labeling for older products more informative for health care practitioners.

DATES: This rule is effective June 30, 2006. See section III of this document for the implementation dates of this final rule.

FOR FURTHER INFORMATION CONTACT:

For information on drug product labeling: Janet Norden, Center for Drug Evaluation and Research (HFD-40), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4202, Silver Spring, MD 20993-0002, 301-796-2270, nordenj@CDER.FDA.GOV, or Elizabeth Sadove, Center for Drug

Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041, sadovee@CDER.FDA.GOV.

For information on labeling of biological products that are regulated as prescription drugs: Toni M. Stifano, Center for Biologics Evaluation and Research (HFM-600), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20856, 301-827-6190, stifano@CBER.FDA.GOV, or Kathleen Swisher, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-827-6210.

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I. Background

In the *Federal Register* of December 22, 2000 (65 FR 81082), FDA issued a proposed rule to revise its regulations governing the content and format of labeling for human prescription drug products, which appear in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57).¹

A. FDA-Approved Prescription Drug Labeling

A prescription drug product's FDA-approved labeling (also known as "professional labeling," "package insert," "direction circular," or

¹ Although §§ 201.56 and 201.57 do not specifically mention the term "biologics", under the Federal Food, Drug, and Cosmetic Act (the act), most biologics are drugs that require a prescription and thus are subject to these regulations. (See section VII of this document for legal authority.) For the purposes of this document, unless otherwise specified, all references to "drugs" or "drug products" include human prescription drug products and biological products that are also drugs.

"package circular") is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. This labeling contains information necessary for safe and effective use. It is written for the health care practitioner audience, because prescription drugs require "professional supervision of a practitioner licensed by law to administer such drug" (section 503(b) of the act [21 U.S.C. 353(b)]). FDA-approved labeling is defined in section 201(m) of the act (21 U.S.C. 321(m)) and is subject to all applicable provisions of section 502 of the act (21 U.S.C. 352). It satisfies the requirement of § 201.100(d) (21 CFR 201.100(d)) that "[a]ny labeling, as defined in section 201(m) of the act * * * that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug * * * contains * * * [a]dequate information for such use," as further described in that provision. FDA-approved labeling also accompanies "promotional" materials, as described in § 202.1(l)(2) (21 CFR 202.1(l)(2)). FDA-approved labeling also "bears adequate information" within the meaning of § 201.100(c)(1), which applies to "labeling on or within the package from which a prescription drug is to be dispensed", referred to in this document as "trade labeling." In this document, FDA-approved labeling for prescription drugs is referred to as "labeling" or "prescription drug labeling."

B. Developing the Proposed Rule

In recent years, there has been an increase in the length, detail, and complexity of prescription drug labeling, making it harder for health care practitioners to find specific information and to discern the most critical information. Before issuing the proposal, the agency evaluated the usefulness of prescription drug labeling for its principal audience to determine whether, and how, its content and format could be improved. The agency used focus groups, a national physician survey, a public meeting, and written comments to develop multiple prototypes and to ascertain how prescription drug labeling is used by health care practitioners, what labeling information practitioners consider most important, and how practitioners believed labeling could be improved. The agency developed a prototype based on this accumulated information as the model for the proposed rule.

C. The Proposed Rule

The agency's proposed changes were designed to enhance the ability of health care practitioners to access, read, and use prescription drug labeling.

1. Proposed Provisions for New and Recently Approved Drugs

FDA proposed the following changes for the labeling for prescription drugs that were approved on or after the effective date of the final rule, drugs that had been approved in the 5 years before the effective date of the final rule, and older approved drugs for which an efficacy supplement is submitted. FDA believed that applying the revised content and format requirements only to more recently approved products was appropriate because, among other reasons, health care practitioners are more likely to refer to the labeling of recently approved products (see comment 113).

- The addition of introductory prescribing information, entitled "Highlights of Prescribing Information" (Highlights).
- The addition of a table of contents.
- Reordering and reorganizing to make the labeling easier to use and read.
- Minimum graphical requirements for format.
- Certain revisions to the content requirements, such as modifying the definition of "adverse reaction" to make the "Adverse Reactions" section of labeling more meaningful and useful to health care practitioners.

2. Proposed Provisions for Older Approved Drugs

The agency proposed that older approved drug products would not be subject to these proposed changes. These older products would, instead, be subject to the labeling requirements at

proposed § 201.80. The agency proposed to redesignate then-current § 201.57 as § 201.80 to describe labeling requirements for older drugs and add new § 201.57 to describe labeling requirements for new and recently approved drugs.

3. Proposed Provisions for All Drugs

FDA also proposed certain revisions to the requirements governing the content of labeling to help ensure that statements appearing in labeling related to effectiveness or dosage and administration are sufficiently supported. These provisions would have applied to all drugs.

- The labeling for all drugs would contain all FDA-approved patient labeling (i.e., approved printed patient information and Medication Guides) for the drug, not just the information required by regulation to be distributed to patients (see table 2).
- Minor revisions would be made to the requirements for labels affixed to prescription drug containers and packaging.

The proposal called for the submission of comments by March 22, 2001. At the request of the Pharmaceutical Research and Manufacturers of America, and to provide all interested persons additional time to comment, the comment period was reopened until June 22, 2001 (66 FR 17375, March 30, 2001). After careful consideration of the comments, FDA has revised the proposal and is issuing this final rule.

The following sections of this document provide:

- An overview of the final rule including changes to the proposed rule (section II of this document).
- A discussion of the implementation requirements for the final rule (section III of this document).

- An overview of the agency's prescription drug labeling initiatives (section IV of this document).
- The implications of this rule for the electronic labeling initiative (section V of this document).

- A discussion of the comments received on the proposal and the agency's responses to the comments (section VI of this document).

- A statement of legal authority (section VII of this document).
- A description of the information collection provisions of the rule (section VIII of this document).
- An statement on the environmental impact of the rule (section IX of this document).

- A statement on federalism (section X of this document),

- An analysis of the economic impacts of the rule (section XI of this document).

- A statement on the impact of the rule on the civil justice system (section XII of this document), and

- A list of references (section XIII of this document).

II. Overview of the Final Rule Including Changes to the Proposed Rule

This final rule amends part 201 (21 CFR part 201) of FDA regulations by revising the requirements for the content and format of labeling for prescription drug products (see tables 1 and 2 of this document). Table 1 lists the sections required for prescription drug labeling before the effective date of this final rule (and which will remain in effect for older products), and, for new and recently approved products, the sections FDA proposed in 2000 and those required by this final rule.

BILLING CODE 4160-01-S

Table 1.--Prescription Drug Labeling Sections

Sections Required for All Products Before the Effective Date of the Final Rule and for Older Products On and After the Effective Date of the Final Rule	Sections That Were Proposed for New and Recently Approved Products	Sections Required for New and Recently Approved Products On or After the Effective Date of the Final Rule
<p>Description</p> <p>Clinical Pharmacology</p> <p>Indications and Usage</p> <p>Contraindications</p> <p>Warnings</p> <p>Precautions</p> <p>Adverse Reactions</p> <p>Drug Abuse and Dependence</p> <p>Overdosage</p> <p>Dosage and Administration</p> <p>How Supplied</p> <p>Optional:</p> <ul style="list-style-type: none"> Animal Pharmacology and/or Animal Toxicology Clinical Studies References 	<p>Highlights of Prescribing Information</p> <ul style="list-style-type: none"> Product Names, Other Required and Optional Information Boxed Warning Recent Labeling Changes Indications and Usage Dosage and Administration How Supplied Contraindications Warnings/Precautions Drug Interactions Use in Specific Populations <p>Comprehensive Prescribing Information: Index</p> <p>Comprehensive Prescribing Information</p> <ul style="list-style-type: none"> 1 Boxed Warning 1 Indications and Usage 2 Dosage and Administration 3 How Supplied/Storage and Handling 4 Contraindications 5 Warnings/Precautions 6 Drug Interactions 7 Use in Specific Populations 8 Adverse Reactions 9 Drug Abuse and Dependence 10 Overdosage 11 Description 12 Clinical Pharmacology 13 Nonclinical Toxicology 14 Clinical Studies R References P Patient Counseling Information 	<p>Highlights of Prescribing Information</p> <ul style="list-style-type: none"> Product Names, Other Required Information Boxed Warning Recent Major Changes Indications and Usage Dosage and Administration Dosage Forms and Strengths Contraindications Warnings and Precautions Adverse Reactions Drug Interactions Use in Specific Populations <p>Full Prescribing Information: Contents</p> <p>Full Prescribing Information</p> <ul style="list-style-type: none"> 1 Boxed Warning 2 Indications and Usage 3 Dosage and Administration 4 Contraindications 5 Warnings and Precautions 6 Adverse Reactions 7 Drug Interactions 8 Use in Specific Populations 9 Drug Abuse and Dependence 10 Overdosage 11 Description 12 Clinical Pharmacology 13 Nonclinical Toxicology 14 Clinical Studies 15 References 16 How Supplied/Storage and Handling 17 Patient Counseling Information

The final rule requires that any FDA-approved patient labeling either: (1) Accompany the prescription drug labeling or (2) be reprinted at the end of such labeling (§§ 201.57(c)(18) and 201.80(f)(2)). Table 2 lists the

requirement in effect before the effective date of this final rule, the 2000 proposed requirement, and the final requirement (see comment 92 for discussion of FDA-approved patient labeling). For the purposes of this document, the term

"FDA-approved patient labeling" will be used to refer to any approved printed patient information or Medication Guide, unless a comment is addressing one or the other specifically.

TABLE 2.—FDA-APPROVED PATIENT LABELING WITH PRESCRIPTION DRUG LABELING

Requirement for All Products Before the Effective Date of the Final Rule	Proposed Requirement for All Products	Final Requirement for All Products
To be reprinted at the end of labeling: • Full text of FDA-approved patient labeling that is required to be distributed to patients	To be reprinted at the end of labeling: • Full text of any FDA-approved patient labeling	To be reprinted at the end of labeling or to accompany the labeling: • Full text of any FDA-approved patient labeling

In this rulemaking, the agency finalizes many of the provisions in the December 2000 proposal. In addition, the final rule reflects revisions the agency made in response to comments on the December 2000 proposal and revisions made by the agency on its own initiative. FDA also has made editorial changes to clarify provisions, correct cross-references, and support the agency's plain language initiative. Table 3 lists the substantive changes made to the general provisions and Highlights and table 4 lists the substantive changes made to the Full Prescribing Information (FPI).

A. Content and Format of Labeling for New and More Recently Approved Prescription Drug Products

The final rule, like the proposed rule, requires that the labeling for new and more recently approved drug products comply with revised content and format requirements (§ 201.56(d)) (see table 1). Like the proposed rule, the final rule provides that new and more recently approved products include drug products with an NDA, BLA, or efficacy supplement that: (1) Was approved between June 30, 2001, and June 30, 2006; (2) is pending on June 30, 2006; or (3) is submitted anytime on or after June 30, 2006 (§ 201.56(b)(1)).

On its own initiative, the agency added a provision on pediatric risk information to the general labeling requirements of the final rule. Section 11 of the Best Pharmaceuticals for Children Act (Public Law 107-109) (BPCA), which was signed into law on January 4, 2001, addresses labeling requirements for generic versions of

drugs with pediatric patent protection or exclusivity. The agency added a provision in § 201.56(d)(5) of the final rule to make clear that any risk information from the "Contraindications," "Warnings and Precautions," or "Use in Specific Populations" section is "pediatric contraindications, warnings, or precautions" within the meaning of section 11 of the BPCA (21 U.S.C. 355A(l)(2)). By adding § 201.56(d)(5), the agency intends to avoid any possible confusion as to what information the agency may require in generic labeling that otherwise omits a pediatric indication or other aspect of labeling pertaining to pediatric use protected by patent or exclusivity.

In addition, the agency declined to adopt the use of symbols that were proposed to emphasize or identify information in prescription drug labeling. Based on comments, FDA declined to use the inverted black triangle (see comment 15) and the exclamation point (!) to emphasize the boxed warning (see comment 43). On its own initiative, for the same reasons that FDA rejected use of the two symbols commented upon, FDA declined to use the following three proposed symbols:

- The Rx symbol (proposed § 201.57(a)(3)) in Highlights. The agency proposed the symbol to identify a product that is available only by prescription, under section 503(b) of the act. The agency decided that the Rx symbol in Highlights is unnecessary because the new prescription drug labeling format is so distinct from the over-the-counter (OTC) drug labeling format that it will be clear to prescribers

that labeling in the new format is for a prescription drug product.

- The "R" symbol in the FPI (proposed § 201.56(d)(2)), which would have identified the "References" section.
- The "P" symbol in the FPI (proposed § 201.57(c)(18)), which would have identified the "Patient Counseling Information" section.

1. Highlights of Prescribing Information

Like the proposed rule, the final rule requires that the labeling for new and more recently approved products include introductory information entitled "Highlights of Prescribing Information" (Highlights) (§§ 201.56(d)(1) and 201.57(a)) (see table 1).

The final rule requires the same headings for Highlights as proposed, except that, in response to comments, FDA moved "Most Common Adverse Reactions" from "Warnings and Precautions" (proposed § 201.57(a)(10)) to a new heading entitled "Adverse Reactions" (§§ 201.56(d)(1) and 201.57(a)(11)) (see table 1 and comment 28). Like the proposed rule, the final rule requires that Highlights, except for the boxed warning, be limited in length to one-half of the page (§ 201.57(d)(8)) (see comment 104).

The agency is also revising its regulations on supplements and other changes to an approved application in §§ 314.70 and 601.12 (21 CFR 314.70 and 601.12) to require applicants to obtain prior approval of any labeling changes to Highlights, except for identified minor changes (see comment 5).

TABLE 3.—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE: GENERAL PROVISIONS AND TO HIGHLIGHTS

21 CFR Section in Final Rule	Description of Change from Proposed Rule
	See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
201.55, 201.57(c)(4)(v), 201.57(c)(12)(l)(D), and 201.100(b)	Container Labels • Withdrew proposed amendments regarding content of container labels and associated proposed amendments to the labeling (106 and 107)

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TABLE 3.—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE: GENERAL PROVISIONS AND TO HIGHLIGHTS—Continued

21 CFR Section In Final Rule	Description of Change from Proposed Rule
	See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
201.56(a)(2)	General Requirement • Revised to clarify that the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading (114)
201.58(d)	Product Title • Deleted proposed § 201.58(d)(4), which permitted a "Product Title" section to be included at the beginning of the FPI (39)
201.56(d)(4)	Format of Contents • Revised to require that the Contents identify if sections have been omitted (37)
201.56(d)(5)	Pediatric Risk Information • Added, on its own initiative, a provision to make clear that pediatric risk information within the meaning of the BPCA may be located in the "Use in Specific Populations" section (11A)
201.57 and 201.80	Unsubstantiated Claims • Removed the 1-year implementation requirement for provisions in §§ 201.57 and 201.80 that prohibit inclusion of unsubstantiated claims in labeling (114)
201.57	Promotional Labeling • Removed, on its own initiative, the reference to statements made in promotional labeling and advertising in proposed 201.57(a) (111)
201.57(a)(1)	Highlights Limitation Statement • Moved the Highlights limitation statement to the beginning of Highlights (35)
201.57(a)(3)	Inverted Black Triangle Symbol • Instead of an inverted black triangle symbol, labeling will state the "Initial U.S. Approval" date (15)
201.57(a)(4)	Boxed Warning • Revised to require that Highlights contain a concise summary of any boxed warning in the FPI (16)
201.57(a)(5)	Recent Labeling Changes • Changed the heading to "Recent Major Changes" and revised to identify only substantive changes to the "Boxed Warning," "Indications and Usage," "Dosage and Administration," "Contraindications," and "Warnings and Precautions" sections and the date of the change(s) (18–22)
201.57(a)(6)	Indications and Usage • Revised to require identification of the pharmacologic class of the drug if it is a member of an established pharmacologic class (6)
201.57(a)(8)	How Supplied • Changed the heading to "Dosage Forms and Strengths" (41)
201.57(a)(11)	Adverse Reactions • Moved "Most Common Adverse Reactions" from "Warnings and Precautions" to a new heading: "Adverse Reactions" (28) • Revised the criteria used for determining which adverse reactions to include in Highlights and that the criteria used be specified (28) • Revised to require that the adverse reactions reporting contact statement be included under the "Adverse Reactions" heading of Highlights; deleted proposed § 201.57(c)(6)(v) that would have required that this statement also be included in the FPI (28 and 30) • Revised the requirements associated with the adverse reactions reporting contact statement (31 and 32)
201.58	Waiver Provision • Revised to make clear applicants can request waivers from any requirement under §§ 201.56, 201.57, and 201.80 (104)

2. Full Prescribing Information: Contents

Like the proposed rule, the final rule requires that the labeling for new and recently approved products include, after Highlights, a list of headings and subheadings contained in the FPI

preceded by the numerical identifier for the heading or subheading (§ 201.57(b)). FDA has revised, on its own initiative, the heading for this portion of the labeling to read "Full Prescribing Information: Contents" (Contents) instead of proposed "Comprehensive Prescribing Information: Index." FDA

made this change for editorial reasons to correctly reflect the function of the section. In response to comments, FDA added certain format requirements for the Contents (see table 3 and comments 37 and 101).

3. Full Prescribing Information

FDA has revised, on its own initiative, the heading for this portion of the labeling to read "Full Prescribing Information" instead of proposed "Comprehensive Prescribing Information." FDA made this change to more accurately reflect that this portion of prescription drug labeling contains the information that FDA determined is necessary for the safe and effective use of the drug, but may not contain all known information about the drug (e.g., details of all clinical trials).

The final rule revises the requirements for the content and format of the FPI in former §§ 201.56(d) and 201.57 for new and recently approved

products (see tables 1 and 2). The final rule establishes minimum requirements for key graphic elements, including bold type, bullet points, type size, spacing and use of vertical and horizontal lines. The final rule requires the same sections for the labeling of these products as proposed except the major, substantive changes listed in table 4, which the agency made in response to comments and, in a few cases as noted, on its own initiative. In addition, FDA made revisions, none of which changed substantive requirements, to the "Dosage and Administration," "Indications and Usage," "Overdosage," "Clinical Pharmacology," and "Drug Interactions" sections. FDA made these changes in response to comments that

requested FDA to clarify these proposed requirements.

In addition, FDA has revised, on its own initiative, "Contraindications" to emphasize that the section must only describe situations in which the potential risks associated with drug use outweigh any possible benefit. FDA believes that including relative or hypothetical hazards diminishes the usefulness of the section. For clarity and emphasis, FDA is requiring that "none" be stated when no contraindications are known. Similarly, FDA deleted, on its own initiative, proposed § 201.57(c)(9)(iii) because it was redundant with requirements in "Warnings and Precautions" and "Contraindications."

TABLE 4.—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE: FULL PRESCRIBING INFORMATION

21 CFR Section In Final Rule	Description of Change From Proposed Rule
	See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
201.57(c)(3)	Dosage and Administration • Revised to make clear that this section must include dosing recommendations based on clinical pharmacologic data, certain dosage modifications, and specified compliance information (51-54)
201.57(c)(4) and 201.57(c)(17)	How Supplied/Storage and Handling • Reorganized information in proposed "How Supplied/Storage and Handling" (§ 201.57(c)(4)) such that the information is now contained in two sections: § 201.57(c)(4) retitled "Dosage Forms and Strengths" and "How Supplied/Storage and Handling" at § 201.57(c)(17) (41)
201.57(c)(7)	Adverse Reactions • Moved the "Adverse Reactions" section (proposed § 201.57(c)(9)) to follow "Warnings and Precautions" (38) • Withdrawn the proposed definition of adverse reaction and retained the definition at former § 201.57(g) (designated in this final rule at § 201.80(g)), with a minor modification (68) • Revised the requirements on how to classify and categorize adverse reactions and how to describe adverse reaction rates (71-75) • Revised to require a description of the overall adverse reaction profile based on entire safety database (70 and 77)
201.57(c)(9)	Use In Specific Populations • Withdrawn the proposed warning statements at §§ 201.57(c)(8)(i)(A)(4) and (c)(8)(i)(A)(5) for pregnancy categories D and X and will continue to require the warning statements at former §§ 201.57(f)(1)(d) and (f)(6)(i)(e) be used (66) • Withdrawn the proposed revisions for the "Nursing Mothers" subsection at § 201.57(c)(8)(iii) and will continue to use the language at former § 201.57(f)(8) (66)
201.57(c)(13)(ii) and 201.80(b)(2)	In Vitro Data for Anti-infectives • Deferred action on proposed §§ 201.57(c)(13)(ii) and 201.80(b)(2) that would have only permitted in vitro data for anti-infective drugs not shown by adequate and well-controlled studies to be pertinent to clinical use be included in labeling if a waiver was granted (81)
201.57(c)(18) and 201.80(f)(2)	Patient Counseling Information • Revised to require that the full text of FDA-approved patient labeling either accompany labeling or be reprinted at the end of the labeling and clarified the type size requirements that apply (93 and 94) (see table 7)
201.57(d)(6)	Font size • Revised to require that font for trade labeling be a minimum of 6-point type instead of 8-point type (t02)
201.57(c)(16) and 201.80(l)	References • Clarified requirements for including a reference (89)

B. Content and Format for Older Prescription Drug Products

Like the proposed rule, the final rule redesignates former § 201.57 as § 201.80. New § 201.80 provides content and format requirements for labeling of older prescription drug products (older products) that are not subject to the labeling requirements at new § 201.57 (see tables 1 and 2).

Section 201.80 is the same as former § 201.57 with the following exceptions that are the same as the changes for new and more recently approved products:

- Modifications that help ensure that statements currently appearing in labeling for older products relating to effectiveness or dosage and administration are sufficiently supported (§ 201.80(c)(2)(i), (c)(2)(ii), (j), and (m)(1)).
- Deletion of proposed § 201.80(b)(2) regarding in vitro data for anti-infectives (see table 4 and comment 81).
- Deletion of "induced emesis" as an example of treatment procedures in the "Overdosage" section of labeling.
- Revisions that allow manufacturers the option of either reprinting the FDA-

approved patient labeling immediately following the last section of the prescription drug labeling or having it accompany such labeling (§ 201.80(f)(2)) (see table 4 and comment 93).

- Addition of the font size provision to redesignated § 201.80(f)(2) (on the agency's own initiative with modifications made in response to comments) (see table 4 and comments 93 and 94).

C. Content of Prescription Drug Product Labels

FDA has reconsidered its proposal to revise the requirements for the content of prescription drug product labels (proposed §§ 201.55 and 201.100(b)). In response to comments, FDA has decided to withdraw these proposed revisions at this time (see comments 106 and 107). The agency had proposed to move certain information about inactive ingredients and storage conditions from the product label to the prescription drug labeling and to remove the requirement to include the statement "See package insert for dosage."

"information" on the product label in cases when it is currently required to be used. These proposed requirements (proposed § 201.57(c)(4)(v) and (c)(12)(i)(D)) were also withdrawn.

The agency intends to conduct a comprehensive evaluation of information required to be contained on product labels. If necessary, FDA will propose changes to these requirements after that evaluation has been completed.

III. Implementation

The final rule is effective June 30, 2006. The final rule has the same implementation plan as proposed for the revised labeling content and format requirements at §§ 201.56(d) and 201.57 for new and more recently approved products (see table 5). Manufacturers of older products that voluntarily elect to revise the format and content of their labeling to be consistent with §§ 201.56(d) and 201.57 may submit a supplement with proposed labeling at any time (see table 5).

TABLE 5.—IMPLEMENTATION PLAN

Applications (NDAs, BLAs, and Efficacy Supplements) Required to Conform to New Labeling Requirements	Time by Which Conforming Labeling Must Be Submitted to the Agency for Approval
Applications submitted on or after June 30, 2006	Time of submission
Applications pending on June 30, 2006 and applications approved 0 to 1 year before June 30, 2006	June 30, 2009
Applications approved 1 to 2 years before June 30, 2006	June 30, 2010
Applications approved 2 to 3 years before June 30, 2006	June 30, 2011
Applications approved 3 to 4 years before June 30, 2006	June 30, 2012
Applications approved 4 to 5 years before June 30, 2006	June 30, 2013
Applications approved more than 5 years before June 30, 2006	Voluntarily at any time

As indicated in the proposed rule, the implementation plan for revised labeling for products approved or submitted for approval under an ANDA depends on the labeling of the listed drug referenced in the ANDA. In accordance with § 314.94(a)(8) (21 CFR 314.94(a)(8)), the labeling of a drug product submitted for approval under an ANDA must be the same as the labeling of the listed drug referenced in the ANDA, except for changes required because of differences approved under a suitability petition (§ 314.93 (21 CFR 314.93)) or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

As the agency proposed (65 FR at 81099), the provisions requiring FDA-approved patient labeling to accompany labeling (§§ 201.57(c)(18) and 201.80(f)(2) of the final rule) will be implemented by June 30, 2007. The agency clarified this provision at §§ 201.57 and 201.56(e)(6).

IV. Overview of Agency Initiatives to Improve the Content and Format of Prescription Drug Labeling

The agency is engaged in a broad effort to improve the communication to health care practitioners of information necessary for the safe and effective use of prescription drugs. A major component of this effort is improvement of the content and format of prescription

drug labeling to make the information in labeling easier for health care practitioners to access, read, and use.

Elsewhere in this issue of the Federal Register, the agency is announcing the availability of four guidance documents on content and format of labeling.² These guidances are intended to assist manufacturers and FDA reviewers in developing clear, concise, and

² The agency announces the availability of guidances in the Federal Register. Draft and final guidances for the Center for Drug Evaluation and Research (CDER)-related information are posted on the Internet at <http://www.fda.gov/cder/guidance/index.htm>. The Center for Biologics Evaluation and Research (CBER)-related information is posted at <http://www.fda.gov/cber/guidelines.htm> (21 U.S.C. 371(h), 21 CFR 10.115).

accessible prescription drug labeling. The four guidances are as follows:

1. A draft guidance entitled "Labeling for Human Prescription Drug and Biological Products—Implementing the New Content and Format Requirements" (the new labeling format guidance). This guidance, which is intended to assist manufacturers in complying with the provisions of this final rule, includes, among other things, how to determine what information from the FPI should be included in Highlights.

2. A draft guidance entitled "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format" (the "Warnings and Precautions" section guidance).

3. A guidance entitled "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format" (the "Adverse Reactions" section guidance). The agency issued a draft of this guidance on June 21, 2000 (65 FR 38563).

4. A guidance entitled "Clinical Studies Section of Labeling for Prescription Drug and Biological Products—Content and Format" (the "Clinical Studies" section guidance). The agency issued a draft of this guidance on July 9, 2001 (66 FR 35797).

The agency is also developing two additional guidances on the content and format of specific sections of labeling—the "Clinical Pharmacology" and "Dosage and Administration" sections. In the future, the agency may develop guidance for additional sections of prescription drug labeling, if necessary.

FDA has undertaken additional rulemaking related to prescription drug labeling. The agency published a final rule in the *Federal Register* entitled "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" that became effective on February 4, 2004 (68 FR 6062, February 6, 2003). This rule requires that the labeling for all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use include certain statements about using antibiotics in a way that will reduce the development of drug-resistant bacterial strains. The rule encourages health care practitioners: (1) To prescribe systemic antibacterial drugs only when clinically indicated and (2) to counsel their patients about the proper use of such drugs and the importance of taking them exactly as directed.

The agency is also engaged in an effort to revise the regulations concerning the content and format of the "Pregnancy" subsection of prescription drug labeling (see the notice of a 21 CFR part 15 hearing to discuss the pregnancy category requirements (62 FR 41061, July 31, 1997) and the notice of a public advisory committee meeting to discuss possible changes to pregnancy labeling (64 FR 23340, April 30, 1999)).

V. Implications of This Final Rule for the Electronic Labeling Initiative

Developing standards for the conversion of paper labeling to an electronic format is a high priority for the agency. On December 11, 2003, FDA published its final rule in the *Federal Register* entitled "Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format" (68 FR 69009). The final rule requires the content of prescription drug labeling, including text, tables, and figures, to be submitted to FDA in an electronic format that the agency can process, review, and archive.

The agency views this final rule on the content and format of labeling as an essential step towards the success of its electronic labeling initiative. The labeling format required by this rule for new and more recently approved products should facilitate transition to an electronic format. The agency believes that an electronic version of labeling in the new format, particularly Highlights and Contents, will significantly expand health care practitioners' ability to access information in prescription drug labeling, enable them to rapidly obtain answers to questions for a range of drug products, and ultimately facilitate the development of a comprehensive repository for drug labeling. For example, FDA envisions that an electronic version of the new format will eventually enable health care practitioners to quickly access labeling information for all drugs in a pharmacologic or therapeutic class with a single electronic query.

FDA realizes that this final rule will affect the agency's existing electronic labeling requirements and guidances and will work to ensure consistency with the electronic labeling initiative.³ The agency believes the electronic labeling initiative, in conjunction with this new format for labeling described in

this final rule, could dramatically improve the way practitioners obtain information about prescription drugs and, as a consequence, significantly improve patient care.

VI. Comments on the Proposed Rule

The agency received 97 comments on the December 22, 2000, proposal. Comments were received from prescription drug manufacturers and related companies; trade organizations representing prescription drug manufacturers and other interested parties; professional associations and organizations representing health care practitioners; health care and consumer advocacy organizations; individual physicians, pharmacists, and consumers; and others.

A. General Comments on the Proposed Rule

Most comments expressed broad agreement that prescription drug labeling could be more effective in communicating drug information to health care practitioners and overwhelming support for the agency's goal of improving the content and format of prescription drug labeling to make information easier for health care practitioners to access, read, and use.

Many comments expressed approval of all the major features of the proposal, indicating that the proposed changes represent an important improvement in the organization, clarity, and overall usefulness of prescription drug labeling. For example, there was near universal support for the proposal to place at the front of labeling those sections that practitioners refer to most frequently and consider most important, although some comments recommended sequences slightly different from those proposed by FDA (see section VI.G of this document). There was also broad support for restructuring the old "Precautions" section into new sections devoted to use in specific populations, drug interactions, and patient counseling information and for combining the remainder of the "Precautions" section with the "Warnings" section.

Comments from manufacturers, while strongly supportive of the agency's efforts to improve the content and format of labeling, generally expressed concerns about some of the major elements of the proposal. In particular, as discussed in greater detail in sections VI.C and VI.D of this document, many manufacturers were concerned about the inclusion of Highlights. Manufacturers also expressed concern about the proposed requirements to re-evaluate, within 1 year of the effective

³ See <http://www.fda.gov/cder/guidance/index.htm> under "Electronic Submissions" and <http://www.fda.gov/cber/guidelines.htm> for the most recent guidances on submission of labeling in an electronic format for drug and biological products, respectively.

date of the final rule, all prescription drug labeling to identify and remove any claims for indications and dosing regimens that are not supported by substantial evidence and to remove in vitro data that are not supported by clinical data.

Specific issues raised by the comments and the agency's responses follow.

B. Comments on the Process for Development of the Proposed Rule

As discussed in detail in the preamble to the proposed rule, FDA relied on focus group testing of physicians, a national physician survey, and a public meeting held in 1995 to develop the labeling prototype that was used as the basis for the proposal (65 FR 81082 at 81083 through 81085).

(Comment 1) Several comments questioned the process that FDA used to develop the proposed rule. A number of comments expressed concern that health care practitioners other than physicians were not surveyed or otherwise consulted. Two comments indicated that a majority of pharmacists refer to prescription drug labeling at least once a day. The comments cited a survey finding that the sections most frequently referred to by pharmacists are, in descending order, "Dosage and Administration," "Adverse Reactions," "Contraindications," "Indications and Usage," "Warnings and Precautions," and "How Supplied/Storage and Handling." The comments urged FDA to consult with all relevant audiences to revise prescription drug labeling and labels.

FDA recognizes the important roles that health care practitioners other than physicians play in the health care delivery system and recognizes that prescription drug information is relied upon by health care practitioners other than physicians. The agency focused its research efforts on how physicians use labeling, because they are the principal intended audience (i.e., they use labeling for prescribing decisions). The agency also sought input from all interested parties in the development of the proposed rule, especially those whose use of labeling could be expected to impact patient safety. Panelists and participants in the 1995 public meeting included nurse practitioners, pharmacists, and physician assistants. Their comments and observations directly contributed to refining the third version of FDA's prototype into the version that was the basis for the proposed rule. Moreover, the agency has carefully reviewed and considered all comments received on the proposed rule, which included comments from a

broad range of health care practitioners that rely on prescription drug labeling, and has determined the optimal ordering for labeling sections, as reflected in this final rule.

FDA notes that the sections most commonly referred to by pharmacists in the cited survey are the same as those most commonly referred to by physicians, although in a somewhat different rank order. FDA believes that, although the rank order of the sections is not identical for the two groups, the formatting improvements required by this final rule make the information in these sections readily accessible to all health care practitioners who use prescription drug labeling.

C. Highlights of Prescribing Information—General Comments

FDA proposed to require that prescription drug labeling for products described in proposed § 201.56(b)(1) (i.e., new and more recently approved prescription drug products) contain introductory prescribing information entitled "Highlights of Prescribing Information" (proposed §§ 201.56(d) and 201.57(a)).

(Comment 2) Comments expressed different opinions about the utility and patient care implications of Highlights. Physicians, pharmacists, other health care practitioners, health care advocacy groups, and professional societies and organizations representing health care practitioners expressed unequivocal enthusiasm about and uniform support for Highlights. Manufacturers, with some exceptions, were opposed, or strongly opposed, to the inclusion of Highlights.

Comments supporting Highlights stated that it would be an excellent vehicle for drawing attention to the most important information about a product, a useful and convenient source for quick reminder information in routine prescribing situations, and a useful vehicle to efficiently direct practitioners to the more detailed information in the FPI. Several comments stated that Highlights is probably the most important innovation in the proposed rule. One comment stated that Highlights is the element of the proposal that will most enhance the clinical utility of prescription drug labeling. Several comments stated that by making prescription drug labeling easier to navigate, Highlights would help to make labeling easier for patients and health care practitioners to understand.

Several comments endorsed the Highlights format as a means of making labeling information more accessible. Some comments stated that the

proposed format for Highlights is a good design because it makes use of multiple formats (e.g., text, tables, bulleted lists) and bolded headings, which make the labeling information more accessible. One comment noted that, because Highlights contains pointers to the location of more detailed information in the FPI, the pointers will increase the likelihood that health care practitioners will refer to the FPI. The comment also stated that the user-friendly Highlights format would be likely to increase the frequency with which health care practitioners consult the labeling for drug information and would enhance their ability to use the information.

Comments opposing inclusion of Highlights stated that manufacturers would be forced to pick certain important warnings listed in the FPI for inclusion in Highlights and, because of space limitations, exclude other important information. These comments maintained that, by extracting from the FPI only selected portions of the information needed for safe and effective use, Highlights would omit important information and lack detail and context, and might, therefore, be misleading. They contended that these shortcomings might outweigh any convenience derived from condensing information into Highlights. One comment maintained that the FPI is itself a condensation of a complex body of information and that it is problematic and illogical to try to further condense the information from the FPI into Highlights.

Several comments from manufacturers stated that the limited content of Highlights is of concern because practitioners would have a tendency to rely only on the information in Highlights when making prescribing decisions, even though that information alone would not be an adequate basis for making such decisions. Some of these comments maintained that there is a lack of evidence to support the premise that Highlights will facilitate practitioners' access to more detailed information in the FPI. They asserted that there is a high likelihood that Highlights would be the only part of the labeling read by practitioners.

Another comment stated that, rather than requiring inclusion of Highlights in labeling, the agency and manufacturers should work together to make the FPI better.

FDA has determined that the Highlights provisions of the final rule are an essential element of the agency's efforts to improve the accessibility, readability, and usefulness of information in prescription drug labeling and reduce the number of

adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information. By means of focus group testing, a nationwide physician survey, and a public meeting, the agency carefully evaluated the drug information needs of physicians and ways to best address those needs in prescription drug labeling. Some of the principal findings were that: (1) The relative importance of information in labeling varies, (2) physicians typically refer to labeling to answer a specific question, (3) physicians have considerable difficulty locating the information they need to make prescribing decisions, and (4) physicians strongly prefer to have a separate introductory summary of the most important information contained in the full prescribing information, located at the beginning of labeling, to make it easier to find the information necessary to prescribe the drug safely and effectively (65 FR 81082 at 81083 through 81085; see also Ref. 11). Many of the comments submitted in response to the proposed rule concur with these findings, particularly those from health care practitioners and their organizations.

This preference for highlighting the most important information that is part of a larger body of information is consistent with good risk communication practices and with well-established cognitive principles. The agency employed these principles in designing Highlights.

For example, cognitive research has shown that, because there is a limit to the amount of information that an individual can hold in memory at one time, individuals tend to organize similar information into "chunks": (1) increase the amount of available space in memory and (2) facilitate retrieval of information (Refs. 1 through 3). "Chunking" complex information into smaller, more manageable units makes it easier to remember and process information efficiently and effectively (decreases "cognitive load").

FDA research conducted during development of new rules for OTC drug labeling demonstrated that "chunking" information in a standardized format with graphic emphasis on the most important information helped individuals make correct product use decisions, decreased reading time, and increased the individuals' confidence in their ability to use that information (Ref. 4). This research supports the approach adopted in this final rule for prescription drug labeling.

In designing Highlights, the agency employed established techniques to enhance effective communication of

large amounts of complex information. Highlights summarizes the information from the FPI that is most important for prescribing the drug safely and effectively and organizes it into logical groups, or "chunks," to enhance accessibility, retention, and access to the more detailed information. This design, combined with the use of multiple formats (e.g., tables, bulleted lists) and graphic emphasis (e.g., bolded text), improves visual and cognitive access to the information so that practitioners can more easily find information, and improves recall of the information.

Importantly, Highlights must include identifying numbers indicating where in the FPI to find details of the information that is cited or concisely summarized in Highlights. In the final rule, FDA has revised proposed § 201.57(a)(17) (§ 201.56(d)(3) in the final rule) to require that any information referenced in Highlights, not just subheadings, be accompanied by the identifying number corresponding to the location of the information in the FPI. The agency believes that these identifying numbers will facilitate access to the detailed information in the FPI.

The Highlights design—a broad array of important information in a discrete, visually accessible location—also increases the variety of information that a practitioner is exposed to in a typical labeling referral. That is, the Highlights design increases the likelihood that practitioners will be exposed to and retain critical information about a drug in addition to the information that the practitioner sought in referring to the labeling, such as the recommended dose. The practitioner therefore is likely to know more about a drug after exposure to labeling with Highlights than after exposure to labeling without Highlights. In addition, by making labeling easier to use and an overall better source of drug information, the Highlights design is likely to increase the frequency with which practitioners rely on labeling for prescription drug information. In a survey regarding labeling for vaccines, 71 percent of physicians surveyed indicated that they would increase their use of labeling if a summary of prescribing information were included in labeling (65 FR 81082 et 81084). Highlights should result in health care practitioners being better informed about prescription drugs. Therefore, the agency concludes that prescription drug labeling with Highlights more effectively communicates drug information to prescribers than labeling without Highlights.

(Comment 3) Some comments stated that FDA should do additional testing to determine whether Highlights is necessary to accomplish FDA's goal of making information in prescription drug labeling more useful and accessible or whether the other proposed format changes, without Highlights (i.e., an index, reordering of the sections of the FPI, and enhanced formatting) would be adequate to accomplish the agency's goal. One comment requested that FDA evaluate whether simply reordering the sections of the prescribing information would be adequate to accomplish the agency's goal. Some comments stated that the agency should test whether the proposed format would change prescriber behavior as intended and lead to a reduction in medication errors.

The agency believes it is unnecessary to compare the prototype labeling with Highlights to the prototype labeling without Highlights (i.e., a version with a table of contents, reordered sections in the FPI, and enhanced graphics, or a version with only reordered sections and enhanced graphics). The requirements of this final rule are built on extensive testing conducted by FDA, established principles of cognitive processing, previous research conducted by FDA for OTC drug labeling, and evaluation of comments submitted in response to this proposal. FDA has determined that Highlights, because it will efficiently and effectively convey information about a drug product and will help to facilitate the transition to electronic labeling, is a vital component of the efforts to reduce the numbers of adverse reactions from medication errors due to misunderstood or incorrectly applied drug information.

(Comment 4) In the proposed rule, FDA specifically sought comment on whether, and under what circumstances, it might be inappropriate to include the proposed Highlights in the labeling of a particular drug or drug class.

The vast majority of comments supported Highlights for all products or no products. One comment stated that if the agency retains the requirement to include Highlights, all products required to have the new format should be required to have Highlights. One comment stated it would not be useful to include Highlights if the entire labeling is very short (e.g., one page).

The agency concludes that there should be no exceptions to the Highlights requirement for drugs subject to the new content and format requirements at §§ 201.56(d) and 201.57. The agency acknowledges that prescription drug labeling for some drugs may be very short and that this

may result in short Highlights. However, as discussed previously, the agency has determined that Highlights improves the usefulness, readability, and accessibility of information in prescription drug labeling and is consistent with good risk communication practices.

(Comment 5) Several comments stated that there should be more specific criteria for selecting information for inclusion in Highlights to ensure consistency for all drug products. These comments stated that, without specific criteria, the information in Highlights for different drugs within the same drug class may be different, and these differences could be used to the competitive advantage or disadvantage of some products. Some comments stated that the agency should designate the precise information that must be included in Highlights. One comment said that, for products with class labeling, FDA must designate which class labeling statements must be included in Highlights to ensure consistency among drugs in the class. Another comment stated that the relative importance of drug information, and, as a result, the basis for selecting information for inclusion in the section, can vary depending on a drug's indication. The comment maintained that Highlights would have to provide for differences in safety profiles for drugs with multiple indications and those that are used in different populations.

The agency believes that these concerns are not unique to Highlights. The agency agrees that, for a given drug, if there are significant differences in safety profiles or dosing considerations for different indications or populations, Highlights must reflect these differences. The agency also agrees that it is critical to ensure accuracy and consistency in the information included in Highlights because it contains a summary of the most important information for prescribing the drug safely and effectively.

In general, however, the agency believes that it would not be appropriate, or possible, to specify in the final rule the precise content of Highlights. Judgment will continue to be necessary to determine what information from the broad range of information necessary for the safe and effective use of the prescription drug appearing in the FPI must also appear in Highlights (e.g., differences in safety profiles or dosing considerations for differing indications or populations). However, because Highlights is a summary of the most important information for prescribing decisions and some comments expressed concerns

about the difficulty involved in summarizing the complex and often lengthy information in the FPI (see e.g., comments 16, 23 and 27), the agency believes that it is essential for FDA to review and approve most proposed changes to the information in Highlights. Accordingly, the agency is revising its regulations on supplements and other changes to an approved application. Under §§ 314.70(b)(2)(v)(C) and (c)(6)(iii), and 601.12(f)(1) and (f)(2)(i), applicants are required to obtain prior approval of any labeling changes to Highlights, except for editorial or similar minor changes, including removal of a listed section(s) from "Recent Major Changes" or a change to the most recent revision date of the labeling. Sections 314.70(d)(2)(x) and 601.12(f)(3)(i)(D) allow these editorial and similar minor changes in the labeling to be reported in an annual report.

In addition, as noted, the agency is making available guidance to assist manufacturers and FDA reviewers in developing prescription drug labeling. This guidance addresses, among other things, how to select information for inclusion in Highlights (section IV of this document).

In some instances, a statement for a drug or class of drugs is currently required by regulation to be included in a specific section of prescription drug labeling (e.g., § 201.21). In these cases, when converting labeling to the new format, the statements must be included in the corresponding section in the new format (e.g., a statement required to be included in the "Boxed Warning" section in the old format must be included in the "Boxed Warning" section in the new format). However, some statements are currently required to be included in labeling sections that have been altered or eliminated by this final rule. In these instances, the statements must be located in the FPI as outlined in table 6.

TABLE 6.—LOCATION OF STATEMENTS REQUIRED TO BE INCLUDED IN LABELING

Location—Old Format	Location—New Format
Warnings	Warnings and Pre-cautions
Precautions (General)	Warnings and Pre-cautions
Precautions (Drug interactions)	Drug Interactions

TABLE 6.—LOCATION OF STATEMENTS REQUIRED TO BE INCLUDED IN LABELING—Continued

Location—Old Format	Location—New Format
Precautions (Specific Populations)	Use in Specific Populations
Precautions (Information for patients)	Patient Counseling Information
How Supplied (or after How Supplied)	How Supplied/Storage and Handling

Where statements are required in labeling but not in a specific labeling section, the agency may specify the location in the FPI for the statements for the drug or class of drugs to ensure consistency within drug classes. Whether a specific statement required by regulation must appear in Highlights will be determined by the agency.

(Comment 6) Several comments stated that Highlights should mention the drug's therapeutic or pharmacologic class. They maintained that this information is informative to practitioners when the drug is a member of an established class because it puts the drug in a context with other therapies and helps prevent duplicative therapy.

The agency agrees that information about a drug's therapeutic or pharmacologic class is important and appropriate for inclusion in Highlights. If a drug is a member of an established therapeutic or pharmacologic class, the identity of that class can provide a practitioner with important information about what to expect from that product and how it relates to other therapeutic options. The agency also agrees with the comment that making the identity of a drug's class more prominent could reduce the likelihood of prescribers placing a patient on more than one therapy within the same class when such use would not be appropriate.

The agency believes that information about drug class is an important supplement to the information contained in a drug's "Indications and Usage" section and should be placed under that heading in Highlights. Accordingly, the agency has revised proposed § 201.57(a)(6) to require that when a drug is a member of an established pharmacologic class, the class must be identified in the "Indications and Usage" section in Highlights.

(Comment 7) One comment stated that Highlights should also include information about managing drug

overdose (recommended a new section entitled "Toxicity and Overdose") and characteristics by which a tablet can be identified (color, markings, shape, etc.).

The agency acknowledges the importance of information about managing drug overdose and characteristics by which a tablet can be identified and took care to make this information prominent in the FPI. However, space for Highlights is limited and the agency has made judgments about which information is most important for safe and effective use and thus must appear in Highlights. The agency has concluded that information about managing overdose or product identification characteristics (except scoring) will not be required in Highlights. The agency has retained scoring in Highlights because this information is needed to appropriately tailor a dose for some patients (e.g., a patient is unable to take two tablets of a drug because of a particular side effect, but is able to take one-and-one-half tablets).

(Comment 8) One comment stated that the information presented in Highlights should be in bulleted format to the extent possible to avoid redundancy with the information in the FPI.

FDA agrees that information presented in Highlights, not otherwise required to be bulleted under § 201.57(d)(4), should be succinctly summarized and in a format (e.g., bulleted) that calls attention, and provides easy access, to the more detailed information in the FPI. Highlights is not a verbatim repetition of selected information contained in the FPI.

(Comment 9) One comment requested that the sections in Highlights be reordered to lend more prominence to risk information. The comment stated that all risk information, including contraindications and drug interactions, should be placed before the "Dosage and Administration" and "How Supplied" sections.

The order of the sections in Highlights tracks the order of the corresponding sections in the FPI. The agency believes the order of information in Highlights must be consistent with the FPI so that practitioners can efficiently navigate from Highlights to the corresponding section of the FPI. As discussed in more detail in the preamble to the proposed rule (65 FR 81082 at 81084), the revised order of the sections in the FPI was based on extensive focus group testing and surveys of physicians to determine which sections they believe are most important to prescribing decisions and

which sections they reference most frequently.

The agency believes that the order of information in Highlights required by the final rule gives sufficient prominence to risk information. The agency also believes that the formatting requirements, the one-half page length restriction for Highlights (excluding space for a boxed warning, if one is required) (§ 201.57(d)(8)), and the limitations on the amount of information that can be included in Highlights will ensure that all the information in Highlights has adequate prominence and is visually accessible.

(Comment 10) One comment expressed concern about the implications of Highlights for FDA's initiative to improve pregnancy labeling. The comment stated that the preliminary format FDA has discussed in public meetings (which would replace the pregnancy category designations) could not be readily condensed into an informative single sentence in Highlights. The comment suggested that electronic labeling could potentially solve this problem by linking to additional information about prescribing in specific patient populations and by linking to pregnancy registry databases and tertiary specialty texts as well.

The agency anticipates that the planned revisions to the requirements for the "Pregnancy" subsection of labeling are unlikely to affect the information in Highlights about use of drugs during pregnancy. The agency agrees that the electronic labeling initiative holds great promise for providing rapid access to related information of varying levels of complexity and detail, including information about drug exposure during pregnancy.

(Comment 11) Several comments recommended that there be an educational campaign in conjunction with the publication of the final rule to ensure that practitioners understand that Highlights contains only limited information and should not be relied on without reference to the FPI.

The agency agrees that there should be, and it plans to initiate, an educational campaign to familiarize health care practitioners with the new labeling format. The agency also agrees that an important component of the educational message should be that Highlights alone does not contain all the information FDA has determined is needed to use a drug safely and effectively.

D. Comments on Product Liability Implications of the Proposed Rule

In the proposal, FDA requested comments on the product liability implications of revising the labeling for prescription drugs.

(Comment 12) In comments, some manufacturers expressed concerns that, by highlighting selected information from the FPI to the exclusion of information not highlighted, they make themselves more vulnerable to product liability claims. Some of these comments also stated that the Highlights limitation statement, which states that Highlights does not contain all the information needed to prescribe a drug safely and effectively and that practitioners should also refer to the FPI, would not constitute an adequate legal defense in a case alleging failure to provide adequate warning of a drug's risks.

Based on the agency's research and analysis in developing the prototype labeling that was the basis for the proposed rule (see comment 2), the agency has concluded that a labeling format that includes Highlights is more effective than a format that omits Highlights. In response to the comments and as discussed in the response to comment 35, FDA has taken steps to enhance the prominence of the Highlights limitation statement. FDA believes the statement will be effective in reminding prescribers that the information in the Highlights should not be relied on exclusively in making prescribing decisions and that it is important to consult the more detailed information in the FPI. We also believe that this limitation statement will help to ensure that the labeling will be considered in its entirety in any product liability action. FDA acknowledges the comment's concerns and, as discussed more fully in response to comment 13, believes that under existing preemption principles such product liability claims would be preempted.

(Comment 13) Some comments stated that the new format requirements might have product liability implications for drugs that are not subject to the new requirements. These comments expressed concern that labeling in the old format might be characterized by plaintiffs as inferior to labeling in the new format and, as a result, could be used as evidence that a manufacturer did not provide adequate warnings. They requested that the agency state in the final rule that FDA approval of labeling, whether it be in the old or new format, preempts conflicting or contrary State law, regulations, or decisions of a

court of law for purposes of product liability litigation.

FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law. Indeed, the Department of Justice (DOJ), on behalf of FDA, has filed a number of amicus briefs making this very point. In order to more fully address the comments expressing concern about the product liability implications of revising the labeling for prescription drugs, we believe it would be useful to set forth (in some detail) the arguments made in those amicus briefs. The discussion that follows, therefore, represents the government's long standing views on preemption, with a particular emphasis on how that doctrine applies to State laws that would require labeling that conflicts with or is contrary to FDA-approved labeling.

Under the act, FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading. Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (21 U.S.C. 355(d)). FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use. FDA continuously works to evaluate the latest available

scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate.

Changes to labeling typically are initiated by the sponsor, subject to FDA review, but are sometimes initiated by FDA. Under FDA regulations, to change labeling (except for editorial and other minor revisions), the sponsor must submit a supplemental application fully explaining the basis for the change (§§ 314.70 and 601.12(f) (21 CFR 314.70 and 601.12(f))). FDA permits two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)); and (2) "changes being effected" (CBE) supplements, which may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)). While a sponsor is permitted to add risk information to the FPI without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the act (21 U.S.C. 352). Thus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling. As noted in response to comment 5, however, a sponsor may not use a CBE supplement to make most changes to Highlights.

Since the proposed rule was published, FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act. In one case, for example, an individual plaintiff claimed that a drug manufacturer had a duty under California State law to label its products with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated.⁴ In some

⁴ *Dowhal v. SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).

⁵ E.g., *Ellis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002), off'd on other grounds, 387 F.3d 1018 (8th Cir. 2004).

⁶ E.g., *Bernhardt v. Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 18963 (S.D.N.Y. Nov. 18, 2000). This doctrine allows a court to refer a matter to an administrative agency for an initial determination where the matter involves technical questions of fact and policy within the agency's jurisdiction. If a court finds that the agency has primary jurisdiction, the court stays the matter and instructs the plaintiff to initiate an action with the agency. See, e.g., *Israel v. Baxter Labs., Inc.*, 485 F.2d 272, 283 (D.C. Cir. 1972); see also 21 CFR 10.80.

of these cases, the court determined that the State law claim could not proceed, on the ground that the claim was preempted by Federal law,⁵ or was not properly before the court by operation of the doctrine of primary jurisdiction.⁶ In some cases, however, the court has permitted the claim to proceed.⁷

State law actions can rely on and propagate interpretations of the act and FDA regulations that conflict with the agency's own interpretations and frustrate the agency's implementation of its statutory mandate. For example, courts have rejected preemption in State law failure-to-warn cases on the ground that a manufacturer has latitude under FDA regulations to revise labeling by adding or strengthening warning statements without first obtaining permission from FDA. (See, e.g., *Eve v. Sandoz Pharm. Corp.*, 2002 U.S. Dist. LEXIS 23965 (S.D. Ill. Jan. 28, 2002); *Ohler v. Purdue Pharma, L.P.*, 2002 U.S. Dist. LEXIS 2368 (E.D. La. Jan. 22, 2002); *Motus v. Pfizer Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000); *Bansmer v. Smith Labs., Inc.*, 1988 U.S. Dist. LEXIS 16208 (E.D. Wis. Sept. 12, 1988); *McEwen v. Ortho Pharm Corp.*, 528 P.2d 522 (Ore. 1974).) In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act. A manufacturer may, under FDA regulations, strengthen a labeling warning, but in practice manufacturers typically consult with FDA before doing so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action).

Another misunderstanding of the act encouraged by State law actions is that FDA labeling requirements represent a minimum safety standard. According to many courts, State law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act. (See, e.g., *Brochu v. Ortho Pharm. Corp.*, 842 F.2d 652 (1st Cir. 1981); *Salmon v. Parke-Davis and Co.*, 520 F.2d 1359 (4th Cir. 1975); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill.

⁷ *Dowhal v. SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004); *Bernhardt v. Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 18963 (S.D.N.Y. November 16, 2000); *Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), summary judgment granted, 198 F. Supp. 2d 984, 988 (C.D. Cal. 2001), aff'd, 2004 U.S. App. LEXIS 1944 (8th Cir. February 9, 2004); *In re Paxil Litigation*, 2002 U.S. Dist. LEXIS 16221 (C.D. Cal. August 18, 2002), transferred, 288 F. Supp. 2d 1374 (J.P.M.L. 2003).

2001); *Mozur v. Merck & Co., Inc.*, 742 F. Supp. 239 (E.D. Pa. 1990); *In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989).) In fact, FDA interprets the act to establish both a "floor" and a "ceiling," such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading. Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

State law requirements can undermine safe and effective use in other ways. In the preamble accompanying the proposal, FDA noted that liability concerns were creating pressure on manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects (65 FR 81082 at 81083). FDA has previously found that labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to "lose its significance" (44 FR 37434 at 37447, June 26, 1979). Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health. (See section X of this document.) Similarly, State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act. (See, e.g., *Dowhal v. SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002) (allowing to proceed a lawsuit involving a California State law requiring warnings in the labeling of nicotine replacement therapy products that FDA had specifically found would misbrand the products under the act), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).)

State law actions also threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs. State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they

encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA—sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief—including the threat of significant damage awards or penalties—that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

FDA has previously preempted State law requirements relating to drugs in rulemaking proceedings. For example:

- In 1982, FDA issued regulations requiring tamper-resistant packaging for OTC drugs. In the preamble accompanying the regulations, FDA stated its intention that the regulations preempt any State or local requirements that were "not identical to * * * [the rule] in all respects" (47 FR 50442 at 50447, November 5, 1982).
- In 1986, FDA issued regulations requiring aspirin manufacturers to include in labeling a warning against use in treating chicken pox or flu symptoms in children due to the risk of Reye's Syndrome. In the accompanying preamble, FDA said the regulations preempted "State and local packaging requirements that are not identical to it with respect to OTC aspirin-containing products for human use" (51 FR 8180 at 8181, March 7, 1986).
- In 1994, FDA amended 21 CFR 20.63 to preempt State requirements for the disclosure of adverse event-related information treated as confidential under FDA regulations (59 FR 3944, January 27, 1994). (See also 47 FR 54750, December 3, 1982) ("FDA believes that differing State OTC drug pregnancy-nursing warning requirements would prevent accomplishment of the full purpose and objectives of the agency in issuing the regulation and that, under the doctrine of implied preemption, these State requirements are preempted by the regulation as a matter of law.")

As noted previously, DOJ has made submissions to courts in a number of cases in which private litigants asserted a State law basis for challenging the adequacy of risk information provided by manufacturers for drugs in accordance with FDA requirements under the act. In each case, DOJ argued

that the doctrine of preemption precluded the plaintiff's claim from proceeding.⁸ The practice of addressing conflicting State requirements through participation in litigation (including product liability cases) in which the Government is not a party is not new. For example, DOJ participated on FDA's behalf in favor of pre-emption in *Jones v. Roth Packing Company*, 430 U.S. 519 (1977), *Grocery Manufacturers of America, Inc. v. Gerace*, 755 F.2d 993 (2d Cir. 1985), *Eli Lilly & Co., Inc. v. Morshall*, 850 S.W.2d 155 (Tex. 1993), and *Buckmon Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001). FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated. In such cases, including the statement in labeling or advertising would render the drug misbranded under the act (21 U.S.C. 352(a) and (f)). The agency believes that State law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling. By complying with the State law in such a case and removing the statement from labeling, the firm would be omitting a statement required under § 201.100(c)(1) as a condition on the exemption from the requirement of adequate directions for use, and the omission would misbrand the drug under 21 U.S.C. 352(f)(1). The drug might also be misbranded on the ground that the omission is material within the meaning of 21 U.S.C. 321(n) and makes the labeling or advertising misleading under 21 U.S.C. 352(a) or (n).

Consistent with its court submissions and existing preemption principles, FDA believes that at least the following

⁸ The DOJ submissions in these cases relied on the doctrine of implied preemption or primary jurisdiction. Although the act itself contains no general express pre-emption provision for drugs, a provision of legislation amending the drug provisions addresses the relationship of the legislation to State law. Section 202 of the Drug Amendments of 1962 (Public Law 87-781, Title II, section 202, 76 Stat. 793 (October 10, 1962)) provides: "Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." The existence of a legislative provision addressing pre-emption does not bar the operation of ordinary principles of implied preemption (*Geier v. American Honda Motor Co., Inc.*, 529 U.S. 881, 890 (2000)).

claims would be preempted by its regulation of prescription drug labeling: (1) Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling; (2) claims that a drug sponsor breached an obligation to warn by failing to include in an advertisement any information the substance of which appears anywhere in the labeling, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the "brief summary" in direct-to-consumer advertising ("Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements," 69 FR 6308 (February 2004)) (see comment 112); (3) claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in this rule, including § 201.57(c)(5) (requiring that contraindications reflect "[k]nown hazards and not theoretical possibilities") and (c)(7); (4) claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning before plaintiff claims the sponsor had the obligation to warn); (5) claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising; and (6) claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label (unless FDA has made a finding that the sponsor withheld material information relating to the statement). Preemption would include not only claims against manufacturers as described above, but also against health care practitioners for claims related to dissemination of risk information to patients beyond what is included in the labeling. (See, e.g., *Bowman v. Songer*, 820 P.2d 1110 (Col. 1991).)

FDA recognizes that FDA's regulation of drug labeling will not preempt all State law actions. The Supreme Court has held that certain State law requirements that parallel FDA requirements may not be preempted (*Medtronic, Inc. v. Lohr*, 518 U.S. 470,

495 (1996) (holding that the presence of a State law damages remedy for violations of FDA requirements does not impose an additional requirement upon medical device manufacturers but "merely provides another reason for manufacturers to comply with * * * federal law"); *id.* at 513 (O'Connor, J., concurring in part and dissenting in part); *id.*). *But see Buckman Co. v. Plaintiffs' Legol Comm'n*, 531 U.S. 341, 352–53 (2001) (holding that "fraud on the FDA" claims are preempted by Federal law); 21 U.S.C. 337(a) (restricting the act enforcement to suits by the United States); *In re Orthopedic Bone Screw Prods. Liability Litig.*, 159 F.3d 817, 824 (3d Cir. 1998) ("Congress has not created an express or implied private cause of action for violations of the FDCA or the MDA (Medical Device Amendments)").

E. Highlights—Comments on Specific Provisions

The agency received comments on the following provisions of the proposed rule relating to the content of Highlights:

- *Drug names, dosage form, route of administration, and controlled substance symbol (proposed § 201.57(o)(1))*

In proposed § 201.57(a)(1), FDA specified the information concerning the identity of the product that would be included at the beginning of Highlights.

(Comment 14) One comment recommended that this information be moved above the title "Highlights of Prescribing Information" in Highlights.

The agency does not agree that the information required by § 201.57(a)(1) should be placed above the title "Highlights of Prescribing Information." The agency believes that the title of each of the three major portions of prescription drug labeling ("Highlights of Prescribing Information," "Full Prescribing Information: Contents," and "Full Prescribing Information") should be placed at the beginning of the corresponding information so that the title is readily apparent to users.

- *Inverted black triangle (proposed § 201.57(a)(2))*

FDA proposed to require that products that contain a new molecular entity, new biological product, or new combination of active ingredients have in their labeling an inverted black triangle to indicate that the drug or drug combination had been approved in the United States for less than 3 years (proposed § 201.57(a)(2)). This proposal also applied to marketed products approved for a new indication, for use

by a new route of administration, or with a novel drug delivery system.

(Comment 15) Several comments opposed, or expressed reservations about, the use of an inverted black triangle to identify a product, indication, or dosage form that has been approved for less than 3 years. There were concerns that the symbol is not universally understood and could therefore be confusing to practitioners. One comment stated that use of icons to convey public health information has historically been unsuccessful. Some of the comments stated that if the inverted black triangle were retained, the agency would need to conduct an extensive educational campaign to educate practitioners about its meaning and purpose. Some comments also expressed the concern that labeling containing the symbol could be in circulation much longer than 3 years after approval, which would undermine the significance of the symbol. One comment stated that the symbol implies, without basis, that newer drugs are inherently less safe than older drugs. Some comments stated that the criteria for when a new indication would extend the time for which a product must have the inverted black triangle are not clear.

Two comments stated that a bold approval date might be more informative than the inverted black triangle. Another comment recommended using the designation "New-Rx" to identify a product that has been approved for less than 3 years.

Other comments expressed strong support for the inverted black triangle as a mechanism to prompt practitioners to more carefully scrutinize the labeling of newer products and more diligently report adverse events. The comments maintained that use of the inverted black triangle could lead to earlier detection of rare, serious adverse reactions and, thus, could potentially save lives. One comment suggested extending the time that the inverted black triangle would be required to 5 years.

The agency has reconsidered its proposal to require use of the inverted black triangle to identify products that have been marketed for less than 3 years. The agency continues to believe strongly in the goals of the inverted black triangle—to help ensure that prescribers use a product with particular care during its initial years of marketing and to make prescribers more diligent in reporting suspected adverse reactions for newer products. However, the agency agrees with comments that, in prescription drug labeling, the inverted black triangle is not universally

EXHIBIT K

--- F.3d ----
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 (Cite as: --- F.3d ----, 2008 WL 927848)

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Colacicco v. Apotex Inc.
 C.A.3 (Pa.), 2008.

United States Court of Appeals, Third Circuit.
 Joseph C. COLACICCO, Individually and as Executor of the Estate of Lois Ann Colacicco, Deceased, Appellant
 v.

APOTEX INC.; Apotex Corp., as Subsidiary of Apotex, Inc.; Smithkline Beecham, d/b/a GlaxoSmithKline

Beth Ann McNellis, on Behalf of the Estate of Theodore DeAngelis, Deceased and in Her Own Right

v.

Pfizer Inc.; John Does 1-5; ABC Doe Corp.; DEF Doe Corp.; GHI Doe Corp.

Pfizer Inc., Appellant.

Nos. 06-3107, 06-5148.

Argued Dec. 10, 2007.

Filed April 8, 2008.

Background: Surviving family members of consumers who had committed suicide after taking medication from class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) brought separate state- and federal-court products liability actions against brand-name and generic drug manufacturers, individually and on behalf of consumers' estates, alleging, *inter alia*, failure to warn of increased risk of adult suicidality. Defendant manufacturer in state-court action removed it. The United States District Court for the Eastern District of Pennsylvania, 432 F.Supp.2d 514, Michael M. Baylson, J., granted manufacturers' motion to dismiss, and surviving family member appealed. The United States District Court for the District of New Jersey, 2005 WL 3752269, Jerome B. Simandle, J., denied manufacturer's motion for summary judgment, and manufacturer sought interlocutory appeal. Cases were consolidated.

Holdings: The Court of Appeals, Sloviter, Circuit Judge, held that:

- (1) presumption against preemption was applicable, but with reduced force;
- (2) survivors' actions were impliedly preempted due to conflict with Food and Drug Administration's (FDA) regulatory actions; and
- (3) FDA's informal position concerning preemption was entitled to some degree of deference.

Affirmed in part and reversed in part.

Ambro, Circuit Judge, filed dissenting opinion.

West Headnotes

[1] Federal Courts 170B ↗763.1

170B Federal Courts

170BVIII Courts of Appeals

170BVIII(K) Scope, Standards, and Extent

170BVIII(K)1 In General

170Bk763 Extent of Review Dependent on Nature of Decision Appealed from

170Bk763.1 k. In General. Most Cited Cases

Court of Appeals applies plenary review over district courts' determinations as to whether federal law preempts state tort claims.

[2] States 360 ↗18.3

360 States

360I Political Status and Relations

360I(B) Federal Supremacy; Preemption

360k18.3 k. Preemption in General. Most Cited Cases

Situations in which federal law preempts state law under Supremacy Clause are: (1) express preemption, applicable when Congress expressly states its intent to preempt state law; (2) field preemption, applicable when Congress' intent to preempt all state law in particular area may be inferred because scheme of federal regulation is sufficiently comprehen-

hensive, or federal interest is so dominant that federal system will be assumed to preclude enforcement of state laws on same subject; and (3) conflict preemption, applicable when state law is nullified to extent that it actually conflicts with federal law, even though Congress has not displaced all state law in given area. U.S.C.A. Const. Art. 6, cl. 2.

[3] Products Liability 313A ↪77

313A Products Liability

313AI Actions

313Ak75 Presumptions and Burden of Proof

313Ak77 k. Particular Products. Most Cited Cases

States 360 ↪18.65

360 States

360I Political Status and Relations

360I(B) Federal Supremacy; Preemption

360k18.65 k. Product Safety; Food and Drug Laws. Most Cited Cases

Presumption against preemption was applicable in state-law products liability actions against manufacturers of antidepressant medications alleging failure to warn of increased risk of suicidality, in which manufacturers asserted implied conflict preemption based on Food and Drug Administration (FDA) labeling regulations; however, force of presumption was reduced by tension between presumption and implied conflict preemption. Federal Food, Drug, and Cosmetic Act, § 505(a-b), 21 U.S.C.A. § 355(a-b); 21 C.F.R. §§ 201.57(e), 314.70(c) (2003).

[4] States 360 ↪18.5

360 States

360I Political Status and Relations

360I(B) Federal Supremacy; Preemption

360k18.5 k. Conflicting or Conforming Laws or Regulations. Most Cited Cases

Conflict between state and federal law, resulting in preemption of state law under Supremacy Clause, arises when compliance with both federal and state

regulations is physical impossibility, or when state law stands as obstacle to accomplishment and execution of full purposes and objectives of Congress. U.S.C.A. Const. Art. 6, cl. 2.

[5] Products Liability 313A ↪46.2

313A Products Liability

313AI Scope in General

313AI(B) Particular Products, Application to

313Ak46 Health Care and Medical Products

313Ak46.2 k. Drugs in General. Most Cited Cases

States 360 ↪18.65

360 States

360I Political Status and Relations

360I(B) Federal Supremacy; Preemption

360k18.65 k. Product Safety; Food and Drug Laws. Most Cited Cases

State-law products liability actions against manufacturers of certain class of antidepressant medications, alleging failure to warn of increased risk of adult suicidality, conflicted with and therefore were impliedly preempted by Food and Drug Administration's (FDA) statutorily authorized regulatory actions, namely its approval of labeling for medications without warning sought by products liability plaintiffs, and its active and consistent refusal to require such warning. U.S.C.A. Const. Art 6, cl. 2; Federal Food, Drug, and Cosmetic Act, §§ 301(b), 505(d)(7), (e)(3), 21 U.S.C.A. §§ 331(b), 355(d)(7), (e)(3); 21 C.F.R. §§ 314.80(c, j), 314.81(b)(2)(i), (d); §§ 201.57(e), 314.70(c)(2)(i) (2003).

[6] Products Liability 313A ↪46.2

313A Products Liability

313AI Scope in General

313AI(B) Particular Products, Application to

313Ak46 Health Care and Medical Products

313Ak46.2 k. Drugs in General. Most Cited Cases

States 360 ↘ 18.65

360 States

360l Political Status and Relations

360l(B) Federal Supremacy; Preemption

360k18.65 k. Product Safety; Food and Drug Laws. Most Cited Cases

Food and Drug Administration's (FDA) informal position concerning preemption, that its statutorily authorized labeling regulations conflict-preempted failure-to-warn products liability actions against manufacturers of antidepressant medications, was entitled to *Skidmore* deference; agency's position was based on its view, entitled to deference, that imposition of liability under state law for manufacturers' alleged failure to warn "would interfere" with FDA's regulatory objectives.

[7] States 360 ↘ 18.9

360 States

360l Political Status and Relations

360l(B) Federal Supremacy; Preemption

360k18.9 k. Federal Administrative Regulations. Most Cited Cases

Federal agency's position concerning preemption of state-law claims need not be contained in formal regulation in order to be considered by court in deciding preemption issue.

*255 Harris L. Pogust, Derek T. Braslow (Argued), T. Matthew Leckman, Pogust & Braslow, Conshohocken, PA, Attorneys for Appellant, No. 06-3107.

M. Karen Thompson, Norris, McLaughlin & Marcus, Sommerville, NJ, Malcolm E. Wheeler (Argued), Wheeler, Trigg & Kennedy Denver, CO, Attorneys for Appellant, No. 06-5148.

Charles A. Fitzpatrick, III, Arthur B. Keppel (Argued), Rawle & Henderson, Philadelphia, PA, Attorneys for Appellee Apotex Corp., Apotex Corp. as Subsidiary of Apotex, No. 06-3107.

Chilton D. Varner (Argued), Andrew T. Bayman, Erica M. Long, S. Samuel Griffin, King & Spalding, Atlanta, GA, Joseph E. O'Neil, Lavin, O'Neil, Ricci, Cedrone & DiSipio, Philadelphia, PA, Attorneys for Appellee Smithkline Beecham, d/b/a

GlaxoSmithKline, No. 06-3107.

Gregory S. Spizer, Sol H. Weiss (Argued), Anapol, Schwartz, Weiss, Cohan, Feldman & Smalley, Philadelphia, PA, Attorneys for Appellee Beth Ann McNellis, No. 06-5148.

Allison Zieve, Public Citizen Litigation Group Washington, DC, Attorney for Amicus-Appellants Public Citizens Litigation Group, Trial Lawyers for Public Justice and Association of Trial Lawyers of America, No. 06-3107.

Shanin Specter, David J. Caputo, Charles L. Becker (Argued), Kline & Specter, Philadelphia, PA, Attorneys for Amicus-Appellant Pennsylvania Trial Lawyers Association, No. 06-3107.

Frederick S. Longer, Arnold Levin, Matthew C. Gaughan, Levin, Fishbein, Sedran & Berman, Philadelphia, PA, Attorneys for Amicus-Appellants Michael H. Alderman, Jerry Avorn, Lisa Bero, Elizabeth A. Boyd, Adriane Fugh-Berman, and Curt D. Furberg, No. 06-3107.

Arnold A. Vickery, Vickery & Waldner, Houston, TX, Attorney for Amicus-Appellants Steve Hulley, Richard A. Kronmal, Kirby Lee, Arthur A. Levin, Bruce M. Psaty, Wayne Ray, Jacquelyn Giles and Annabel Dobbs, No. 06-3107.

Michael A. Galpern, Law Offices of Gene Locks, Cherry Hill, NJ, Attorney for Amicus-Appellees Association of Trial Lawyers of America-New Jersey, No. 06-5148.

Kenneth S. Geller, Mayer, Brown, Rowe & Maw, Washington, DC, Attorney for Amicus-Appellees Product Liability Advisory Council, Inc., No. 06-3107.

Robert N. Weiner, Jeffrey L. Handwerker, Arnold & Porter, Washington, DC, Attorneys for Amicus-Appellees Pharmaceutical Research and Manufacturers of America, No. 06-3107.

Michael X. Imbroscio, Covington & Burling Washington, DC, Attorney for Amicus-Appellees American Tort Reform Association, No. 06-3107.

Douglas N. Letter, Sharon Swingle (Argued), United States Department of Justice, Washington, DC, Attorneys for Amicus-Appellee United States, No. 06-3107.

Before: SLOVITER, AMBRO, Circuit Judges, and RESTANI ^{FN*}, Judge.

FN* Hon. Jane A. Restani, Chief Judge, United States Court of International Trade, sitting by designation.

*256 OPINION OF THE COURT

SLOVITER, Circuit Judge.

*1 The issue before us is one of preemption, an area of the law that need delicately balance federal interests and those of the states. It harks back to the very beginning of our republic, and has continued to occupy us ever since. Preemption is not a doctrine that lends itself to a black-letter rule. One size does not fit all. The decision must be based on the circumstances presented in the particular situation.

The plaintiffs in these consolidated cases are the husband and daughter, respectively, of two adults who committed suicide after taking medication from the class of antidepressants known as selective serotonin reuptake inhibitors ("SSRIs"). The common question presented by the cases is whether the plaintiffs may maintain their state-law tort actions against the manufacturers of two such drugs on the theory that the drugs' labeling failed to warn of their association with an increased risk of suicidality. The central issue is whether actions taken by the Food and Drug Administration ("FDA") pursuant to its authority under the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301-397, and the corresponding regulatory scheme preempt the plaintiffs' state-law failure-to-warn claims.

I.

SmithKline Beecham, d/b/a GlaxoSmithKline ("GSK"), manufactures Paxil, an SSRI that is used to treat depression. On October 6, 2003, Lois Colacicco's physician prescribed Paxil for her depression. After her prescription was filled with a

generic version of Paxil, Lois Colacicco began taking that medication. Less than a month later, on October 28, 2003, at the age of fifty-five, she committed suicide in her New York home.

At the time of Lois Colacicco's death, the labeling for Paxil included the following language in its "Precautions" section:

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose....

Colacicco App. at 436. Apotex, Inc. and Apotex Corp. (together, "Apotex") manufacture and distribute the generic version of paroxetine hydrochloride (the active ingredient in Paxil) ingested by Lois Colacicco. The labeling for Apotex's generic paroxetine was identical to GSK's labeling for Paxil.

After Lois Colacicco's death, her husband, Joseph C. Colacicco, filed suit against Apotex and GSK in the United States District Court for the Eastern District of Pennsylvania, alleging that those companies violated state common-law tort rules and New York state consumer protection laws by selling their products with labels that failed to warn consumers of the increased risk of emergent suicidality and worsening depression in adults taking paroxetine. On May 26, 2006, Apotex and GSK moved to have Colacicco's complaint dismissed on the ground that it was preempted by federal law and, alternatively, that GSK did not owe a duty of care to the consumers of generic paroxetine, such as Lois Colacicco. The District Court dismissed the complaint on the basis of preemption. *Colacicco v. Apotex, Inc.*, 432 F.Supp.2d 514, 537-39 (E.D.Pa.2006).

*2 Pfizer is the manufacturer of Zoloft, another SSRI that is used to treat depression. On January

22, 2003, sixty-four-year old Theodore DeAngelis was prescribed *257 Zoloft for anxiety and depression. DeAngelis ingested that drug in the days leading up to his death by suicide on January 30, 2003. At the time of his death, the suicide precaution on Zoloft's labeling read as follows:

Suicide-The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Zoloft (sertraline) should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

McNellis App. 499-500.

Following DeAngelis' death, Beth Ann McNellis, his daughter and the executrix of his estate, filed suit in New Jersey state court, alleging that Pfizer violated various New Jersey products liability and consumer fraud statutes by selling Zoloft without warning consumers that it increased the risk of suicidality in those ingesting the drug. Pfizer removed the action to the United States District Court for the District of New Jersey and moved for summary judgment on the ground that McNellis' claim was preempted by federal law. The Court denied that motion on December 29, 2005. *McNellis ex rel. DeAngelis v. Pfizer, Inc.* ("McNellis I"), No. Civ. 05-1286(JBS), 2005 WL 3752269, at *13 (D.N.J. Dec.29, 2005). On September 29, 2006, following the dismissal of Colacicco's complaint in the Pennsylvania District Court, the New Jersey District Court denied Pfizer's motion to vacate its denial of the summary judgment motion, but certified its order for interlocutory appeal. The District Court framed the question for appeal as follows:

Whether ... the United States Food and Drug Administration's requirements for the form and content of the labeling for the prescription antidepressant Zoloft preempted New Jersey's failure-to-warn law, under the doctrine of conflict preemption, where the FDA's regulations at 21 C.F.R.

201.57(e) [(2003)] and 314.70(c)(6)(iii) [(2007)] permit a manufacturer to unilaterally enhance its warning when the manufacturer has reasonable evidence of an association of a serious hazard with a drug.

McNellis ex rel. DeAngelis v. Pfizer, Inc. ("McNellis II"), No. Civ. 05-1286(JBS), 2006 WL 2819046, at *13 n. 9 (D.N.J. Sept.29, 2006). We must decide which of the two fine opinions authored by two of the ablest district judges in this circuit most closely expresses our view of the difficult issue presented.

II.

The FDA is charged with "promot[ing] the public health by promptly and efficiently reviewing [drug manufacturers'] clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and "protect[ing] the public health by ensuring that ... drugs are safe and effective." 21 U.S.C. § 393(b)(1), (b)(2)(B). In this capacity, the FDA regulates the introduction of all new drugs. *Id.*§ 355(a). Persons intending to market a drug must first file a new drug application ("NDA") with the FDA. *Id.*§ 355(b). An NDA must include, *inter alia*, full reports of investigations into the drug's safety and effectiveness, the components and production methods used to manufacture the drug, and "specimens of the labeling proposed to be used for such drug." *Id.*§ 355(b)(1); *see also* 21 C.F.R. § 314.50(c)(2)(i) (requiring manufacturers to include "statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter"), (e)(2)(ii).

*258 *3 Although "labeling" may be commonly understood as the label affixed to a prescription bottle, in this context it also encompasses the written material sent to the physician and included with the drug provided to the patient.^{FNI} The FDA regulations require prescription drug labeling to include "a summary of the most clinically significant information ... critical to safe use of the drug," including, *inter alia*, potential safety hazards associ-

ated with use of the drug. 21 C.F.R. § 201.57a(10), (c)(6)(i). Applicants must also include a “summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.” *Id.* § 314.50(d)(5)(viii).

FN1. “Labeling” is defined by statute as “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” 21 U.S.C. § 321(m). Thus, labeling “embraces advertising or descriptive matter that goes with the package in which the articles are transported,” *Kordel v. United States*, 335 U.S. 345, 350, 69 S.Ct. 106, 93 L.Ed. 52 (1948), in addition to any label that may be placed directly on a pill bottle.

The FDA must deny an NDA if it finds that:

- (1) the investigations [discussed above] do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
- (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; or
- (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.

21 U.S.C. § 355(d). The FDA shall otherwise approve the NDA. *Id.* The “FDA will approve an application and issue the applicant an approval letter ... on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling.” 21 C.F.R. § 314.105(b). However, “[s]uch approval will be conditioned upon the applicant incorporating the

specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.” *Id.*

The FDA’s post-approval oversight of drug labeling is governed primarily by regulation.^{FN2} At the times relevant to this litigation, 21 C.F.R. § 201.56 described the general requirements for the content and format of drug labeling, while 21 C.F.R. § 201.57 set forth the specific requirements for such labeling.^{FN3} Section 201.57(e) *259 required manufacturers to “describe serious adverse reactions and potential safety hazards” under the heading “Warnings.” 21 C.F.R. § 201.57(e) (2003). Moreover, “[t]he labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.” *Id.* The same section states that “[s]pecial problems, particularly those that may lead to death or serious injury, may be required by the [FDA] to be placed in a prominently displayed box.... If a boxed warning is required, its location will be specified by the [FDA].” *Id.*

FN2. Because many of the relevant regulations were revised or relocated after the dates relevant to this litigation (both DeAngelis and Lois Colacicco were prescribed SSRIs and committed suicide between January and October of 2003), we set forth the regulations in effect during that time period in the text and, where applicable, provide parallel citations to the current language and location of those regulations in footnotes. Unless otherwise noted, the substance of the regulations cited in this opinion have remained consistent between January of 2003 and the present.

FN3. As part of the FDA’s amendments to its labeling regulations in 2006, additional labeling requirements for recently approved drugs were added to § 201.56 and that section was retitled. See 21 C.F.R. §

201.56 (2007); *see also* 71 Fed. Reg. 3922, 3986 (Jan. 24, 2006). Meanwhile, the specific requirements relating to drugs introduced prior to the amendments were amended and redesignated as § 201.80. See 71 Fed. Reg. at 3988, 3996. Of primary importance to this litigation, the text formerly appearing at § 201.57(e) now appears at § 201.80(e). The relevant language remains unchanged. Compare 21 C.F.R. § 201.57(e) (2003), with 21 C.F.R. § 201.80(e) (2007). *See also* 71 Fed. Reg. at 3996.

FDA regulations also govern the procedures for revising drug labeling. At all times relevant to this litigation, an applicant was required to notify the FDA of any changes to an approved drug, including its labeling, by one of three methods, depending on the magnitude of the intended change. *See* § 314.70(a)-(d) (2003). Section 314.70(b) covered “supplements requiring FDA approval before the change is made.” *Id.* § 314.70(b). “Any change in labeling, except one described in [subsections] (c)(2) or (d) of this section” required FDA pre-approval. *Id.* § 314.70(b)(3)(i). Subsection (d) was limited to minor changes that may be submitted with the drug manufacturer’s annual report, and is not implicated by this litigation. *See id.* § 314.70(d). Subsection (c), however, described “changes that may be made before FDA approval.” *Id.* § 314.70(c). In particular, “[a]n applicant shall submit a supplement at the time the applicant makes” a change to its labeling “[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction.” *Id.* § 314.70(c)(2)(i). The supplemental submissions by which § 314.70(c) changes are accomplished are sometimes referred to as “changes being effected” or “CBE” supplements.^{FN4}

FN4. The FDA also amended § 314.70 in 2006. The regulation now refers to changes under subsections (b), (c), and (d) as “major,” “moderate,” and “minor” changes, respectively. 21 C.F.R. §

314.70(b), (c), (d) (2007). For the purposes of this litigation, subsections (b) and (d) are not materially different. Subsection (c), however, is now titled “Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).” *Id.* § 314.70(c). Nonetheless, that subsection also states that the FDA “may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change.” *Id.* § 314.70(c)(6). The listed categories include changes in labeling “[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction.” *Id.* § 314.70(c)(6)(iii)(A). Thus, for all practical purposes, subsection (c)(2)(i) has simply been relocated to subsection (c)(6)(iii)(A), but the FDA may determine that products incorporating such labeling changes may not be distributed until the agency has received the CBE supplement or thirty days thereafter. Finally, the FDA now provides express notice that if it “disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.” *Id.* § 314.70(c)(7).

After oral argument, the FDA submitted a proposed rule that would further limit the type of changes that may be effected pursuant to § 314.70(c)(6)(iii). *See* 73 Fed. Reg. 2848 (Jan. 16, 2008). Specifically, that regulation would be limited to: “Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of

this section), to accomplish any of the following: (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c) of this chapter....”⁷³ Fed.Reg. at 2853.

*⁴ Drug manufacturers have continuing obligations to report adverse drug experiences,^{*260} *id.* § 314.80(c), and any “significant new information ... that might affect the safety, effectiveness, or labeling of the drug product,”*id.* § 314.81(b)(2)(i). Failure to abide by these obligations may result in withdrawal of an approved drug. *Id.* §§ 314.80(j), 314.81(d).

Although regulations describe the particulars of the FDA’s oversight of drug labeling, the FDCA describes the primary penalties for a drug manufacturer’s failure to comply with those regulations. The FDA must withdraw approval of a drug if it finds “on the basis of new information before [it] ... that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.” 21 U.S.C. § 355(e). The FDA may withdraw approval of a drug if, “on the basis of new information before [it] ... the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the [FDA] specifying the matter complained of.” *Id.*

The distribution of “misbranded” drugs is also prohibited by the FDCA. *Id.* § 331(a), (b). A drug is misbranded if its “labeling is false or misleading in any particular,”*id.* § 352(a), if its labeling lacks “adequate warnings against use ... where its use may be dangerous to health,”*id.* § 352(f), or if “it is dangerous to health when used in the ... manner ... prescribed, recommended, or suggested in the labeling thereof,”*id.* § 352(j). The FDA has the au-

thority to enforce the prohibition on misbranding by initiating injunction proceedings, *see id.* § 332, criminal prosecutions, *see id.* § 333(a), and the seizure of misbranded drugs, *see id.* § 334.

Once a drug has been approved, it is included in the FDA’s published list of approved drugs. *See*²¹ U.S.C. § 355(j)(7). Such a drug is then referred to as a “listed drug.” *Id.* § 355(j)(2)(A)(i). A listed drug is sometimes also referred to as an “innovator” or “pioneer” drug. *See, e.g., Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1494, 1497-98 (D.C.Cir.1996). Although the manufacturers of listed drugs, such as GSK and Pfizer in this case, are governed by all of the requirements associated with NDAs, the manufacturers of generic drugs, such as Apotex, are not required to submit an NDA. Rather, such manufacturers must abide by certain statutes and regulations that are based on the equivalence of generic drugs to the listed drugs.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) relaxed the approval procedures for generic drug manufacturers, allowing them to submit an abbreviated NDA (“ANDA”). Pub.L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(j), 35 U.S.C. §§ 156, 271, 281). An ANDA must contain information showing the generic drug’s bioequivalence to the listed drug and that “the labeling proposed for the new drug is the same as the labeling approved for the listed drug....”²¹ U.S.C. § 355(j)(2)(A)(iv) & (v).^{FN5} FDA regulations also provide that the agency may seek withdrawal of a generic drug, pursuant to notice and the opportunity for a hearing, if “the labeling for the [generic drug] is no longer consistent with that for the listed drug referred to in the [ANDA].”²¹ C.F.R. § 314.150(b)(10).

FN5. The FDA states that generic drug manufacturers may not add new warnings to the approved labeling for the listed drug. 57 Fed.Reg. 17,950, 17,953, 17,955, 17,961 (April 28, 1992).

*261 III.

*5 The District Courts had jurisdiction over the plaintiffs' claims under 28 U.S.C. § 1332. We have jurisdiction over Colacicco's appeal pursuant to 28 U.S.C. § 1291 following the entry of the order of the Pennsylvania District Court dismissing Colacicco's complaint; we have jurisdiction over Pfizer's appeal from the New Jersey District Court's interlocutory order denying Pfizer's motion for summary judgment in McNellis' case because the District Court certified that order pursuant to 28 U.S.C. § 1292(b).

[1] The issue underlying the District Courts' orders presents a question of law. We apply plenary review over their preemption determinations. See *Pennsylvania Employees Benefit Trust Fund v. Zeneca Inc.*, 499 F.3d 239, 242 (3d Cir.2007) (motion to dismiss); *Horn v. Thoratec Corp.*, 376 F.3d 163, 166 (3d Cir.2004) (motion for summary judgment).

IV.

[2] The doctrine of preemption is rooted in the Supremacy Clause, U.S. Const. art. VI, cl. 2, which provides that the "Constitution, and the Laws of the United States which shall be made in Pursuance thereof ... shall be the supreme Law of the Land." Early in our constitutional history, the Supreme Court interpreted this language to invalidate state laws that "interfere with, or are contrary to," federal law, the genesis of the preemption doctrine. *Gibbons v. Ogden*, 22 U.S. (9 Wheat.) 1, 211, 6 L.Ed. 23 (1824). The Supreme Court has identified three major situations where there is preemption. They were described in *Hillsborough County v. Automated Med. Labs., Inc.* as: (1) "express" preemption, applicable when Congress expressly states its intent to preempt state law; (2) "field" preemption, applicable when "Congress' intent to pre-empt all state law in a particular area may be inferred [because] the scheme of federal regulation is sufficiently comprehensive" or "the federal interest is

so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject;" and (3) "conflict" preemption, applicable when "state law is nullified to the extent that it actually conflicts with federal law," even though Congress has not displaced all state law in a given area.^{FN6} 471 U.S. 707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985) (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230, 67 S.Ct. 1146, 91 L.Ed. 1447 (1947)).

FN6. Both field and conflict preemption are sometimes referred to as forms of implied preemption. See, e.g., *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 884, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000); *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S.Ct. 1483, 131 L.Ed.2d 385 (1995). However, the Supreme Court has also asserted that these three categories are not "rigidly distinct;" for example, "field pre-emption may be understood as a species of conflict preemption: A state law that falls within a pre-empted field conflicts with Congress' intent (either express or plainly implied) to exclude state regulation." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79-80 n. 5, 110 S.Ct. 2270, 110 L.Ed.2d 65 (1990).

An express preemption situation is exemplified by the Supreme Court's recent decision in *Riegel v. Medtronic, Inc.*, --- U.S. ----, 128 S.Ct. 999, 169 L.Ed.2d 892 (2008), where it considered the effect of the express preemption provision of the Medical Device Amendments of 1976 ("MDA") to the FDCA.^{FN7} It held that in *262 light of that provision, plaintiffs' claims that an arterial catheter was designed, labeled, and manufactured in a way that violated New York common law were preempted. *Id.* at 1003, 1005, 1011. See also *Horn*, 376 F.3d at 166.

FN7. The statutory language provides that:

no State or political subdivision of a

State may establish or continue in effect with respect to a device intended for human use any requirement (1) which is different from, or in addition to, any requirement applicable under [the MDA] to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under [the Act].

21 U.S.C. § 360(k)(a).

In the *Colacicco* case, the Pennsylvania District Court noted that GSK and Apotex conceded that express and field preemption are not implicated, and proceeded exclusively under a conflict preemption analysis. 432 F.Supp.2d at 523. After reviewing the applicable principles and relevant precedent, and accorded considerable deference to the FDA's position, the Court held that Colacicco's claims are preempted. *Id.* at 537-38. In so holding, the Court rejected Colacicco's argument that the FDA's position should not be accorded deference because it was inconsistent with the FDA's prior statements. The Court concluded that "after 2000, the FDA has been very consistent." *Id.* at 531-32.

*6 A directly contrary conclusion was reached by the New Jersey District Court in the *McNellis* case. In the first of two opinions on the issue, the Court denied defendant Pfizer's motion for summary judgment, holding that it was unwilling to find that Congress intended to obviate the state laws upon which *McNellis*' complaint was based. *McNellis I*, 2005 WL 3752269, at *10. The Court held that discovery was needed on whether Pfizer had reasonable evidence of an association between Zoloft and suicidality. *Id.* at *11. In its opinion the following year, the Court declined to vacate its earlier opinion, and instead determined that "there can be no conflict preemption because the FDA's regulations do not conflict with New Jersey's failure to warn laws." *McNellis II*, 2006 WL 2819046, at *5. The Court held that the interpretation of the FDA was not entitled to the substantial deference accorded by

the Pennsylvania District Court, and certified its order to this court for interlocutory appeal. *Id.* at *10, *13.

The pharmaceutical companies do not seriously argue that this is a case of express preemption^{FN8} or field preemption. We therefore limit our consideration to whether the plaintiffs' state-law claims conflict with the federal scheme.

FN8. Apotex and GSK briefly argue that this is a case of express preemption because the 1962 Amendments to the FDCA stated: "Nothing in the amendments made by this Act to the [FDCA] shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub.L. No. 87-781, § 202, 76 Stat. 780, 793 (Oct. 10, 1962). Of course, the plain language of this provision states that the Amendments do not preempt state law in the absence of a conflict. Thus, to the extent that this provision affects our analysis, it merely states that conflict preemption applies. In other words, this "express preemption" provision simply leads us to a conflict preemption analysis, which may be applied independently of an express preemption analysis.

A.

[3] We consider first whether there is a presumption against preemption applicable in this case. The existence *vel non* of such a presumption is contested. The Supreme Court has stated: "[i]n all preemption cases, and particularly in those in which Congress has legislated in a field which the States have traditionally occupied, we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest *263 purpose of Congress." *Medtronic, Inc. v. Lohr*, 518 U.S.

470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996) (hereafter referred to as “*Lohr*”) (citation, internal quotation marks, and alterations omitted). Colacicco and McNellis emphasize this “presumption against preemption,” and both District Courts recognized the existence of that presumption. See *Colacicco*, 432 F.Supp.2d at 524; *McNellis I*, 2005 WL 3752269, at *3. Although a presumption against preemption is commonly acknowledged, the Supreme Court has made clear that the application of such a presumption is not always appropriate. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-48, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (declining to apply a presumption against preemption where the plaintiff alleged fraud on the FDA).

Apotex and GSK argue that a presumption against preemption does not apply in the circumstances presented here because the states have not traditionally been involved in the regulation of drug labeling, whereas the federal government has regulated that area for over a hundred years. Pfizer takes an even broader position, arguing that the presumption against preemption does not apply at all in conflict preemption cases.^{FN9} The Supreme Court’s decision in *Hillsborough County* undermines both of these arguments. In that case, the Court stated that the “presumption that state or local regulation of matters related to health and safety is not invalidated under the Supremacy Clause,”⁴⁷¹ U.S. at 715, 105 S.Ct. 2371, and then proceeded to analyze whether local regulations imposed on blood plasma centers “conflict with the federal scheme,” *id.* at 720, 105 S.Ct. 2371. The Court concluded that the County’s ordinances and regulations, which imposed donor testing and requirements beyond those contained in the federal regulations, and which were designed to protect the health of the donors, to ensure the quality of the plasma, and to protect the recipients of the plasma, *id.* at 715-16, 105 S.Ct. 2371, were not preempted by the federal regulatory scheme because the County’s requirements “do not imperil the federal goal of ensuring sufficient plasma,”*id.* at 722, 105 S.Ct. 2371.

FN9. Pfizer also argues that it has overcome the presumption were it applicable. Where appropriate, we have not hesitated to find a conflict even after applying the presumption against preemption. See *Fasano v. Fed. Reserve Bank of New York*, 457 F.3d 274, 283, 290 (3d Cir.2006).

*7 The Supreme Court later addressed the presumption against preemption in *Lohr*, where the plaintiff, who was injured by the failure of her pacemaker, filed a “common-law negligence action against the manufacturer of an allegedly defective medical device.” 518 U.S. at 474, 116 S.Ct. 2240. The manufacturer argued that the claim was preempted by a provision in the MDA that bars state or local requirements different from those applicable under the MDA and which relate to the safety or effectiveness of any device covered by the Act.^{FN10} *Id.* at 481, 116 S.Ct. 2240. The Court referred to the states’ police powers to protect the health and safety of their citizens, *id.* at 485, 116 S.Ct. 2240, the premise of the presumption against preemption, in holding that plaintiff’s negligence action was not preempted. A plurality of the Court noted that the statutory language precluded any additional “requirement,” not any “remedy,” under state law, *id.* at 487, 116 S.Ct. 2240, and concluded, by reference to the legislative history, that the statute “was not intended to pre-empt most, let alone all, general common-law duties enforced by damages actions.” *264 *Id.* at 491, 116 S.Ct. 2240. We note, however, that the Court did not discuss the presumption against preemption in its recent opinion in *Riegel* considering the same provision of the MDA at issue in *Lohr*.

FN10. See supra note 7.

There are, as the pharmaceutical companies argue, relevant Supreme Court decisions where the Court explicitly declined to apply any presumption against preemption. In *Buckman*, plaintiffs, who claimed injuries from the use of orthopedic bone screws, brought suit against the consultant to the manufacturer on the theory that its statements de-

frauded the FDA and led the agency to approve a device that caused the plaintiffs' injuries. See 531 U.S. at 343, 347-48, 121 S.Ct. 1012. The Supreme Court held that plaintiffs' fraud claims were preempted. It rejected plaintiffs' argument that there was a "virtually irrefutable presumption against implied preemption of private damage remedies predicated on an alleged conflict with a federal remedial scheme." *Id.* at 351, 121 S.Ct. 1012 (internal quotation marks omitted). Because "the relationship between a federal agency and the entity it regulates ... originates from, is governed by, and terminates according to federal law," the Court concluded that the plaintiffs' claims did not implicate the traditional state interest in the regulation of public health and safety, and thus it did not apply the presumption against preemption. *Id.* at 347-48, 121 S.Ct. 1012.

Similarly, in *United States v. Locke*, 529 U.S. 89, 94, 108, 120 S.Ct. 1135, 146 L.Ed.2d 69 (2000), the Supreme Court considered whether Washington State laws governing oil tanker operations and designs enacted after the oil spill caused by the Exxon Valdez were preempted by a comprehensive federal regulatory scheme governing oil tankers. The Court declined to apply a presumption against preemption because the case concerned "national and international maritime commerce," a field in which "Congress has legislated ... from the earliest days of the Republic." *Id.* The Court noted that "an 'assumption' of nonpre-emption is not triggered when the State regulates in an area where there has been a history of significant federal presence." *Id.*

*8 While the decisions in *Buckman* and *Locke* are distinguishable from the cases before us, they do make clear that it is "the purpose of Congress [as] the ultimate touchstone of pre-emption analysis," *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516, 112 S.Ct. 2608, 120 L.Ed.2d 407 (1992) (citations, internal quotation marks, and alterations omitted), to which we must turn. See also *Rice*, 331 U.S. at 230, 67 S.Ct. 1146; *Fasano v. Fed. Reserve Bank of New York*, 457 F.3d 274, 284 (3d

. Colacicco and McNellis argue that preemption is inappropriate because Congress has never expressed its intent to preempt state-law tort actions challenging drug labeling. McNellis notes that the New Jersey District Court concluded that it was "unwilling to find ... that Congress intended to obviate the very state laws that provide remedies to consumers harmed by dangerous products and deceptive marketing in the absence of a clear and compelling Congressional statement." *McNellis I*, 2005 WL 3752269, at *10 (citing *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 450, 125 S.Ct. 1788, 161 L.Ed.2d 687 (2005)).

The pharmaceutical companies respond by quoting the Supreme Court's statement that "in a situation where state law is claimed to be pre-empted by federal regulation, a 'narrow focus on Congress' intent to supersede state law [is] misdirected,' for '[a] pre-emptive regulation's force does not depend on express congressional authorization to displace state law.' " *265 *City of New York v. FCC*, 486 U.S. 57, 64, 108 S.Ct. 1637, 100 L.Ed.2d 48 (1988) (quoting *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 154, 102 S.Ct. 3014, 73 L.Ed.2d 664 (1982)). In fact, the Supreme Court has found that even where an express preemption saving clause demonstrated Congress' intent to exempt common-law tort actions from preemption, the language of the saving clause did not suggest an intent to "bar the ordinary working of conflict pre-emption principles" or preserve "state-law tort actions that conflict with federal regulations." *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 869, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000). The Court held that federal regulations may preempt common-law tort actions under a conflict preemption analysis despite a statutory provision stating that " '[c]ompliance with' a federal safety standard 'does not exempt any person from any liability under common law.' " *Id.* at 868, 120 S.Ct. 1913 (quoting 15 U.S.C. § 1397(k) (1988 ed.)). Thus, the Court concluded that plaintiff's tort action against the automobile manufacturer for failing to install airbags was preempted under conflict preemption principles although expressly saved

from preemption by statute. *Id.* at 881, 120 S.Ct. 1913.

It follows that in this case, which is also one of conflict preemption, the lack of a Congressional directive expressly approving or rejecting preemption in the context of drug labeling regulations is not determinative. Rather, the conflict preemption analysis is designed to determine the propriety of preemption where Congress has not explicitly stated its intent. Seen in this light, Pfizer's argument that the presumption against preemption is inapplicable in the context of implied conflict preemption has more force. Although the Supreme Court applied the presumption in *Hillsborough County*, a decision in which it engaged in a conflict preemption analysis, that analysis followed the Court's consideration of field preemption principles. 471 U.S. at 716-20, 105 S.Ct. 2371.^{FN11} Therefore, the extent to which the Court relied on the presumption in the context of its conflict analysis is not clear. Here, we recognize the applicability of the presumption against preemption, but note the tension between such a presumption, which emphasizes the "clear and manifest purpose of Congress," *Lohr*, 518 U.S. at 485, 116 S.Ct. 2240 (internal quotation marks omitted), and implied conflict preemption, which analyzes preemption in the absence of any explicit intent, *cf. Geier*, 529 U.S. at 885, 120 S.Ct. 1913 (failing to formally apply the presumption against preemption, but "assum[ing] that Congress or an agency ordinarily would not intend to permit a significant conflict").

FN11. Although both field and conflict preemption are generally thought of as forms of implied preemption, a focus on Congressional intent is of greater value in the context of field preemption, where Congress' mere presence in a given field indiscriminately nullifies all state law in the field, than in the context of conflict preemption, which excludes state law only to the extent that it requires individuals to act contrary to conflicting federal obliga-

tions.

B.

*9 [4] A conflict between state and federal law "arises when compliance with both federal and state regulations is a physical impossibility or when state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hillsborough County*, 471 U.S. at 713, 105 S.Ct. 2371 (citations and internal quotation marks omitted); *see also City of New York*, 486 U.S. at 64, 108 S.Ct. 1637 ("The statutorily authorized regulations of an agency will pre-empt any *266 state or local law that conflicts with such regulations or frustrates the purposes thereof.").

There are not many examples of instances where it is impossible to comply with both federal and state law, presumably because state legislatures and regulators do not readily seek confrontation with federal authority. One such example is provided by the Court's 1913 decision where it considered the effect of a 1907 Wisconsin statute providing that mixtures or syrups offered for sale "shall have upon them no designation or brand ... other than that required by the state law...." *McDermott v. Wisconsin*, 228 U.S. 115, 127, 33 S.Ct. 431, 57 L.Ed. 754 (1913). The federal food and drugs act passed in 1906 barred false and misleading labels on product packages. *Id.* at 127, 129, 33 S.Ct. 431. When the issue came before the Supreme Court, it stated that "the State may not, under the guise of exercising its police power or otherwise, ... enact legislation in conflict with the statutes of Congress passed for the regulation of the subject...." *Id.* at 131-32, 33 S.Ct. 431. The Court held that the state statute was invalid because "[t]he legislative means provided in the Federal law for its own enforcement may not be thwarted by state legislation having a direct effect to impair the effectual exercise of such means." *Id.* at 137, 33 S.Ct. 431.

The scarcity of actual conflict cases has led the Justices to pose hypothetical conflicts. In *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S.

132, 143, 83 S.Ct. 1210, 10 L.Ed.2d 248 (1963), the Supreme Court hypothesized the existence of an impossibility conflict where “federal orders forbade the picking and marketing of any avocado testing more than 7% oil, while the California test excluded from the State any avocado measuring less than 8% oil content.” Under those circumstances, it would be a “physical impossibility” for avocado growers to comply with both federal and state law because California law would require them to do what federal law forbade, that is, pick their avocados after they surpassed the 7% ceiling established by federal law. *Id.*

In another case, where the issue was whether a federal statute that permits national banks to sell insurance in small towns preempts a state statute that forbids them to do so, Justice Breyer discussed the impossibility situation:

In this case we must ask whether or not the Federal and State Statutes are in “irreconcilable conflict.” The two statutes do not impose directly conflicting duties on national banks-as they would, for example, if the federal law said, “you must sell insurance,” while the state law said, “you may not.”

*10 *Barnett Bank of Marion County, N.A. v. Nelson*, 517 U.S. 25, 31, 116 S.Ct. 1103, 134 L.Ed.2d 237 (1996).

Most of the preemption cases falling within the conflict category are cases that present the second scenario discussed in *Hillsborough County*-when “state law stands as an obstacle to the accomplishment and execution of the full purpose and objectives of Congress.” 471 U.S. at 713, 105 S.Ct. 2371 (internal quotation marks omitted). In his opinion in *Barnett Bank*, Justice Breyer continued,

the Federal Statute authorizes national banks to engage in activities that the State Statute expressly forbids. Thus, the State’s prohibition of those activities would seem to “stan[d] as an obstacle to the accomplishment” of one of the

Federal Statute’s purposes-unless, of course, that federal purpose is to grant the bank only a very *limited* permission, that is, permission to sell insurance *to the extent that state law also grants permission to do so*.

*267 517 U.S. at 31, 116 S.Ct. 1103 (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67, 61 S.Ct. 399, 85 L.Ed. 581 (1941)). After deciding that the McCarran-Ferguson Act antipreemption rule did not govern the case, *id.* at 38, 116 S.Ct. 1103, the Court held that the federal statute preempted the state statute, *id.* at 42, 116 S.Ct. 1103.

It is not only state statutes that may stand as obstacles to the achievement of federal objectives. It is now established that law suits based on state tort law, as well as on state statutes, may be viewed as presenting obstacles to the federal objectives and hence barred as preempted. In *Geier*, the Court held that an action against American Honda based on its failure to provide a driver’s side airbag was preempted by a federal regulation. The Court adopted the principle that ordinary preemption principles apply to a state tort action where an actual conflict with a federal objective is at stake. *Geier*, 529 U.S. at 871-72, 120 S.Ct. 1913. The majority stated that in the absence of such a principle:

state law could impose legal duties that would conflict directly with federal regulatory mandates, say, by premising liability upon the presence of the very windshield retention requirements that federal law requires. See, e.g., 49 CFR § 571.212 (1999). Insofar as petitioners’ argument would permit common-law actions that “actually conflict” with federal regulations, it would take from those who would enforce a federal law the very ability to achieve the law’s congressionally mandated objectives that the Constitution, through the operation of ordinary preemption principles, seeks to protect. To the extent that such an interpretation of the saving provision reads into a particular federal law toleration of a conflict that those principles would otherwise forbid, it permits that law to defeat its own ob-

jectives, or potentially, as the Court has put it before, to “‘destroy itself.’”

Id. (quoting *Am. Tel. & Tel. Co. v. Cent. Office Tel., Inc.*, 524 U.S. 214, 228, 118 S.Ct. 1956, 141 L.Ed.2d 222 (1998)).

A similar consideration was noted in *Lohr* where Justice Breyer, in his separate opinion concurring in part and dissenting in part, stated that “ordinarily, insofar as [federal law] pre-empts a state requirement embodied in a state statute, rule, regulation, or other administrative action, it would also pre-empt a similar requirement that takes the form of a standard of care or behavior imposed by a state-law tort action.” 518 U.S. at 504-05, 116 S.Ct. 2240. In *Horn*, which dealt with the same express preemption provision as in *Lohr*, we quoted from the FDA’s letter brief stating, *inter alia*,

*11 State common law tort actions threaten the statutory framework for the regulation of medical devices, particularly with regard to FDA’s review and approval of product labeling. State actions are not characterized by centralized expert evaluation of device regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the balancing of benefits and risks of a specific device to their intended patient population—the central role of FDA—sometimes on behalf of a single individual or group of individuals.

376 F.3d at 178.

State common-law tort actions based on the manufacturers’ failure to warn present the pharmaceutical manufacturers with particular difficulties. State standards of care undoubtedly differ from state to state. Absent a determination that the FDA-approved labeling and the FDA’s refusal to require the warnings suggested by plaintiffs in this case preempt state tort actions, the manufacturers may be subjected to *268 considerable liability based on varying standards, with no benchmark that they should follow.

In holding the tort action based on the failure to provide airbags was preempted, the Court in *Geier* reviewed the history of the consideration of passive restraints by the federal agency, there the Department of Transportation. Similarly, in this case, before we can hold that a federal regulation or, as in *Geier*, the failure to regulate as extensively as plaintiffs sought, has preemptive force, we must review the record of the FDA’s treatment of the desired warning at issue here.

[5] As discussed above, a new drug may not be marketed until it has received FDA approval. The FDA will not approve a drug if its “labeling is false or misleading in any particular.” 21 U.S.C. § 355(d)(7). Even after a drug has been approved, a drug will be deemed misbranded if the “labeling is false or misleading in any particular” and the FDA may withdraw approval of that drug and prosecute the manufacturer. See *id.* §§ 331(b) (prohibition on misbranding), 355(e)(3) (withdrawal authority), 352(a), (f), (j) (definition of misbranding), 332 (injunction proceedings), 333(a) (criminal prosecutions), 334 (seizure). Thus, the FDCA vests the FDA with significant authority over drug labeling. FDA regulations further implement this authority.

Under its regulations, the FDA may withdraw approval of a drug if the manufacturer disregards its obligation to submit periodic reports notifying the FDA of adverse drug experiences and other new information that might affect the drug labeling. 21 C.F.R. §§ 314.80(c), (j), 314.81(b)(2)(i), (d). FDA regulations detail the information that must be included in the warnings section of drug labeling and instruct that such “labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug....” *Id.* § 201.57(e) (2003); *id.* § 201.80(e) (2007).

There are three distinct procedures by which manufacturers may revise their drugs’ labeling, each of which requires the manufacturer to notify the FDA of its proposed revision. See *id.* § 314.70(a)-(d). Generally, labeling changes require FDA pre-

approval. See *id.* § 314.70(b)(3)(i) (2003). However, changes that “add or strengthen a contraindication, warning, precaution or adverse reaction,” may be implemented prior to the manufacturer’s receipt of FDA approval. *Id.* § 314.70(c)(2)(i) (2003); *id.* § 314.70(c)(6)(iii)(A) (2007).

*12 Colacicco and McNellis argue that because § 314.70(c) allows drug manufacturers to strengthen and augment warnings on drug labeling without prior FDA approval, the FDA labeling requirements constitute mere minimum standards for the information that may be required in their labeling. See, e.g., *Sprietsma v. Mercury Marine*, 537 U.S. 51, 58-59, 123 S.Ct. 518, 154 L.Ed.2d 466 (2002). Therefore, they argue that state-law failure-to-warn claims that would require manufacturers to strengthen or augment a warning do not conflict with FDA regulations, and are in fact complementary to those regulations.

The pharmaceutical companies respond that even though labeling changes made pursuant to § 314.70(c) do not require prior approval, the legality of those changes remains within the FDA’s control. They state that because the FDA is directly involved with balancing the benefits and risks of a drug’s labeling, see, e.g., 21 C.F.R. § 314.50(d)(5)(viii), and has the statutory authority to order the manufacturer to discontinue distribution of any products incorporating the manufacturer’s labeling change, the FDA-approved labeling*269 reflects the FDA’s expert judgment about the information that must be included in a drug’s labeling.^{FN12}

FN12. Apotex, for its part, argues that tort actions against generic drug manufacturers are preempted because the Hatch-Waxman Amendments and the FDA’s implementing regulations require such manufacturers to maintain labeling identical to that of the innovator drug.

Of course, in this case we must focus on the effect of the FDA’s failure to require a warning that

plaintiffs argue was the cause of their injury rather than the effect of a positive regulation. It is always easier to evaluate the effect of a conflict created by a positive regulation than the effect created by inaction. It is difficult to know whether the absence of a regulation may reflect a wait-and-see approach or mere inertia. We are guided to some extent by *Geier* where the Court held that the failure of the Department of Transportation to require auto manufacturers to equip their 1997 vehicles with a specific form of passive restraint system, i.e. airbags, preempted the state “no airbag” tort suit. 529 U.S. at 874, 881, 120 S.Ct. 1913.

In this case we need not speculate on the rationale of the FDA for its failure to require the adult suicidality warnings. Not only has the FDA filed an amicus brief in the *Colacicco* action but it has repeatedly rejected the scientific basis for the warnings that Colacicco and McNellis argue should have been included in the labeling. The FDA has actively monitored the possible association between SSRIs and suicide for nearly twenty years,^{FN13} and has concluded that the suicide warnings desired by plaintiffs are without scientific basis and would therefore be false and misleading.

FN13. Colacicco, whose complaint was dismissed prior to discovery, argues that the District Court improperly relied on evidence of the FDA’s past actions and that we are prohibited from considering that information. This problem does not arise in the McNellis case, which is before us following summary judgment proceedings. Of course, courts may place limited reliance on public records in the context of a motion to dismiss. See *Anspach ex rel. Anspach v. City of Philadelphia, Dep’t of Pub. Health*, 503 F.3d 256, 273 n. 11 (3d Cir.2007). Thus, in *Anspach*, we took notice of FDA public records “not for the truth of [their] contents, but rather as evidence of the information provided by the federal government” to the relevant regu-

lated parties. *Id.* Our recognition of the records contested here, all of which are publicly available, is similarly limited. See also *Jean Alexander Cosmetics, Inc. v. L'Oréal USA, Inc.*, 458 F.3d 244, 256 n. 5 (3d Cir. 2006) (recognizing that courts may take judicial notice of prior judicial proceedings).

In 1991, after considering whether antidepressants caused or intensified suicidal thoughts, the FDA's Psychopharmacological Drugs Advisory Committee concluded that no such warning should be added to Prozac (an SSRI similar to Paxil and Zoloft) or other antidepressants. The FDA specifically rejected citizen petitions in 1991, 1992, and 1997 which sought to either withdraw approval of Prozac as a result of its asserted association with suicide or to include a suicide warning on the labeling of that drug. In each instance, the FDA concluded that there was insufficient evidence to take the actions requested.

*13 DeAngelis committed suicide on January 22, 2003. The FDA approved the Zoloft suicide precaution seven separate times before and after that date, in each instance requiring Pfizer to market the drug with the precise labeling approved.^{FN14} Further, *270 just months before DeAngelis' death, the FDA filed an amicus brief in an action before the Court of Appeals for the Ninth Circuit, stating that it had concluded that there was no scientific basis for a warning suggesting that Zoloft causes suicidality. See Brief for the United States as Amicus Curiae, *Motus v. Pfizer Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498), 2002 WL 32303084 (brief submitted September 10, 2002).^{FN15}

FN14. The FDA first approved Zoloft for the treatment of depression in adults on December 30, 1991, conditioning its approval on Pfizer's incorporation of specifically indicated labeling revisions. In 1996, the FDA approved Zoloft for a new indication, the treatment of obsessive compulsive disorder ("OCD"), with that ap-

proval again conditioned on Pfizer's incorporation of a series of labeling revisions. The FDA proceeded to approve the use of Zoloft for panic disorder and pediatric OCD in 1997, post-traumatic stress disorder in 1999, premenstrual dysphoric disorder in 2002, and, on February 7, 2003, social anxiety disorder. Each time the FDA approved Zoloft for a new indication, it required that the final printed labeling be identical to the labeling attached to the FDA's approval.

FN15. The New Jersey District Court acknowledged the FDA's position in *Motus*, but decided that it was not appropriate to defer to that litigation position. See *McNelis I*, 2005 WL 3752269, at * 10. However, we distinguish between the agency's legal position in its amicus brief and its factual representations. In the *Motus* brief, the FDA stated not just its legal conclusions with respect to the applicability of preemption, but it also reported its view of the state of scientific research regarding Zoloft and antidepressants at that time. The FDA's summary of its scientific determinations must be distinguished from the agency's construction of a statute, as the review of scientific information is strictly within its expertise. The FDA asserted facts in support of its legal position, and we take notice of its statement of those facts, rather than its legal position.

The FDA also repeatedly approved the Paxil labeling in effect at the time of Lois Colacicco's prescription of Paxil on October 6, 2003, and her death on October 28, 2003, approving it for a new indication, the treatment of generalized anxiety disorder, just a year before those events.^{FN16} The FDA approved Apotex's application to market generic paroxetine on June 30, 2003, concluding that "the drug is safe and effective for use as recommended in the submitted labeling," which included the suicide

precaution discussed above, rather than a warning. See Letter from Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, to Apotex Corp. 3 (July 30, 2003), available at <http://www.fda.gov/cder/foi/appletter/2003/75356ap.pdf> (last visited January 8, 2008). Significantly, on June 19, 2003, the FDA issued a public statement to address reports associating the pediatric use of Paxil with suicidality, in which it stated: "There is no evidence that Paxil is associated with an increased risk of suicidal thinking in adults." FDA Talk Paper, FDA Statement Regarding the Anti-Depressant Paxil for Pediatric Population (June 19, 2003), available at <http://www.fda.gov/bbs/topics/answers/2003/ans01230.html> (last visited Nov. 8, 2007).

FN16. As with its approvals of Zoloft, the FDA approved Paxil for new indications on the condition that the final drug labeling be identical to the labeling approved by the FDA. See, e.g., Letter from Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research, FDA, to GlaxoSmithKline (Oct. 2, 2002), available at <http://www.fda.gov/cder/foi/appletter/2002/20031se8-035ltr.pdf> (last visited January 8, 2008).

On October 27, 2003, the FDA issued a Public Health Advisory regarding increased suicidality in pediatric users of antidepressants. This advisory was limited to pediatric patients; a warning for adult patients was not issued. In that advisory, the FDA announced that it would continue to research the reports of suicidality in pediatric patients treated with antidepressants, explaining that "[s]uch reports are very difficult to interpret, in the absence of a control group, as these events also occur in untreated patients with depression." FDA, FDA Public Health Advisory (Oct. 27, 2003), available at <http://www.fda.gov/cder/drug/advisory/mdd.htm> (last visited January 8, 2008).

Thus, even when it began to reevaluate its position regarding the association of antidepressants with pediatric and adolescent suicidality, the FDA continued to announce its rejection of adult suicidality warnings for SSRIs as it had for the decade before the prescriptions and deaths at issue in this litigation. Just months prior to Lois Colacicco's death, the FDA publicly stated that Paxil was not associated with a risk of suicidality in adults. Similarly, four months before DeAngelis' death, the FDA filed a public brief stating its position that scientific evidence did not support the addition of a suicide warning on Zoloft's labeling.

*14 Although preemption is commonly thought of in terms of statutes and regulations, a federal agency's action taken pursuant to statutorily granted authority may also have preemptive effect over state law. See *Chicago & N.W. Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311, 327, 101 S.Ct. 1124, 67 L.Ed.2d 258 (1981) ("These findings by the [Interstate Commerce] Commission, made pursuant to the authority delegated by Congress, simply leave no room for further litigation over the matters respondent seeks to raise in state court."); *NCNB Texas Nat'l Bank v. Cowden*, 895 F.2d 1488, 1497-99 (5th Cir.1990) (finding that Federal Deposit Insurance Corporation's action taken pursuant to statutory authority preempted state law); cf. *Spritesma*, 537 U.S. at 66-67, 123 S.Ct. 518 (recognizing that an agency's refusal to regulate may be construed as a determination that no such regulation is appropriate and have preemptive force). Because the standard for adding a warning to drug labeling is the existence of "reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), and the FDCA authorizes the FDA to prohibit false or misleading labeling, a state-law obligation to include a warning asserting the existence of an association between SSRIs and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association. Therefore, under the circumstances of this case, the plaintiffs' failure-to-warn claims are preempted by the FDA's ac-

tions taken in accordance with its statutory authority.

The FDA clearly and publicly stated its position prior to the prescriptions and deaths at issue here. Therefore, we need not decide whether preemption would be appropriate under different facts—such as where the FDA had not rejected the substance of the warning sought or where the FDA only stated its position after a lawsuit had been initiated—or under the broader theories of preemption argued by the parties. Thus, we do not decide whether the FDA's mere approval of drug labeling is sufficient to preempt state-law claims alleging that the labeling failed to warn of a given danger, whether FDA approval of drug labeling constitutes minimum standards in the absence of the FDA's express rejection of a specific warning, or whether actions against generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments.^{FN17} Our holding is *272 limited to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires. Cf. *Dowhal v. SmithKline Beecham Consumer Healthcare*, 32 Cal.4th 910, 12 Cal.Rptr.3d 262, 88 P.3d 1, 11 (2004) (concluding that an FDA “letter established a federal policy prohibiting defendants from giving consumers any warning other than the one approved by the FDA in that letter, and that the use of a [warning required by state law] would conflict with that policy”).

FN17. In contrast to our decision, the Supreme Court of Vermont has held that plaintiffs' negligence and failure-to-warn claims alleging inadequate warnings on the labeling of an anti-nausea drug “did not conflict with the FDA's labeling requirements for [the drug] because [Wyeth] could have warned against [the danger alleged by plaintiffs] without prior FDA approval, and because federal labeling regulations create a floor, not a ceiling, for state regulation.” *Levine v. Wyeth*, 944 A.2d 179, ¶ 6 (Vt.2006), cert. granted, ---

U.S. ----, 128 S.Ct. 1118, 169 L.Ed.2d 845 (2008). The Vermont Court found that there was “no evidence that the FDA intended to prohibit defendant from strengthening the [drug] label pursuant to [§] 314.70(c)” and thus it was not impossible for Wyeth to comply with both state and federal obligations. *Id.* ¶ 23. The facts in these cases are otherwise.

The plaintiffs raise two primary objections to this conclusion. First, they argue that nothing less than the FDA's explicit rejection of a drug manufacturer's request to add a contested warning to its drug labeling should suffice to establish conflict preemption. Second, they contend that the pharmaceutical companies failed to provide the FDA with sufficient information for it to make a valid decision regarding the necessity of a suicidality warning. Neither argument is persuasive.

*15 As we previously noted, the FDA is authorized by statute to reject an NDA if the labeling is false or misleading in any particular and may withdraw its approval of a drug upon the same findings. See 21 U.S.C. § 355(d)(7), (e)(3). Plaintiffs argue, however, that the FDA's actions were insufficient to manifest such a rejection here. They ask us to overlook the FDA's various public statements rejecting the existence of an association between SSRIs and adult suicidality because they were not made in the context of the FDA's formal rejection of a CBE supplement submitted by one of the defendant pharmaceutical companies.

We agree that a court could more easily determine the preemption issue if the FDA had formally rejected such a CBE supplement, but we cannot compel the defendant companies to suggest a CBE supplement that they believe is unnecessary. Nor do we favor encouraging regulated parties to submit CBE supplements for the sole purpose of insulating themselves from potential liability. Cf. 44 Fed.Reg. 37,434, 37,435 (June 26, 1979) (cautioning, in the context of medical malpractice liability, that “it would be inappropriate to require statements in

drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation in which the agency has no part"). Thus, we reject the notion that, in order to rise to the level of a conflict in this situation, the FDA's rejection of a warning must be imbued with the formality proposed by the plaintiffs.

Colacicco further argues that the FDA's failure to require an adult suicidality warning cannot be seen as a rejection of the warning that his lawsuit would require because "GSK manipulated or withheld information from the FDA." Colacicco Reply Br. at 9. This contention borders on the charge that GSK defrauded the FDA by manipulating or withholding such information. Cf. *Buckman*, 531 U.S. at 346-47, 121 S.Ct. 1012. Such a claim, if supported by sufficient evidence, should be brought before the FDA. As far as we know from the record, Colacicco has not done so.

In the New Jersey action, McNellis opposed Pfizer's motion for summary judgment by submitting copies of research studies that were made public, which McNellis argued showed a link between *273 SSRIs and suicidality. McNellis does not argue that the FDA was unaware of this material. Our focus is on the period before the two deaths that are the subject of the actions before us. We note, however, that the FDA has continued its close scrutiny of the effect of SSRI drugs on suicidality of adults. In March of 2004, the FDA directed GSK and nine other manufacturers of SSRIs to include stronger warnings on drug labels about the need to monitor adult patients for signs of worsening depression or suicidality, but noted that it had "not concluded that these drugs cause worsening depression or suicidality in adult patients." FN18 Br. for the United States as Amicus Curiae at 13 (citing FDA Talk Paper, FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children (March 22, 2004), available at <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html>).

FN18. In April 2006, GSK, after reviewing studies that disclosed a higher incidence of suicidal behavior in young adults treated with Paxil, modified its Paxil label to include a warning that young adults "especially those with [major depressive disorder], may be at an increased risk of suicidal behavior when treated with" Paxil. Br. for the United States as Amicus Curiae at 14 (citing Paxil Label, available at <http://us.gsk.com/products/assets/USpaxil.pdf> (last visited Feb. 27, 2008)). It made this change only after filing the proposed change with the FDA and waiting the required 30 days.

*16 More recently, the FDA, after its review of the aggregated data from all SSRI manufacturers, reaffirmed its conclusion that there is insufficient evidence demonstrating that SSRIs are associated with adult suicidality. In its widely distributed notice on Antidepressant Use in Children, Adolescents and Adults dated May 2, 2007, available at <http://www.fda.gov/cder/drug/antidepressants/default.htm> (last visited Feb. 22, 2008), the FDA incorporated its conclusions that "[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24" and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality. Revisions to Product Labeling, available at <http://www.fda.gov/cder/drug/antidepressants/antidepressants-la-label-change-2007.pdf> (last visited Feb. 22, 2008); see also FDA News, FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications, http://www.fda.gov/bbs/topics/NEWS/2007/NEW_0_1624.html (May 2, 2007). FN19 The FDA Revisions to Product Labeling directed the drug companies (including manufacturers of Paxil and Zoloft) to make changes in the warnings included at the beginning of the package inserts that confirm that antidepressants increase the risk of suicidality in children, adolescents, and young adults but that the studies did not

show an increase in the risk of suicidality in adults older than age 24.^{FN20} In light of the FDA's continued*²⁷⁴ review of existing scientific studies, we reject plaintiffs' arguments that the FDA lacked information that would have dissuaded it from rejecting an adult suicidality warning for Zoloft, Paxil, or generic paroxetine in 2003.

FN19. We may, of course, take judicial notice of this development "which [took] place after the judgment appealed from." *Werner v. Werner*, 267 F.3d 288, 295 (3d Cir.2001).

FN20. The entire text of the revised warning reads as follows:

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert Drug Name] is not approved for use in pediatric patients. [The previous

sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use). Revisions to Product Labeling, available at <http://www.fda.gov/cder/drug/antidepressants/antidepressants-label-change-2007.pdf> (last visited Feb. 22, 2008).

[6] The FDA has taken the position, both in the preamble to the 2006 amendments revising the drug labeling regulations and in its amicus brief in the *Colacicco* case, that plaintiffs' claims are preempted as a result of the actions taken by the FDA pursuant to its regulatory authority. The preamble specifically states that preemption applies to "claims that a [manufacturer] breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the [manufacturer] had an obligation to warn." 71 Fed.Reg. 3922, 3936 (Jan. 24, 2006). The FDA explains in the amicus brief that "the basis for federal preemption is not the [labeling] guidelines themselves ..., but rather FDA's repeated determinations prior to October 2003 that there was insufficient scientific evidence of an association between adult use of SSRI and suicide or suicidality to permit a warning on the labeling for those drugs...." Br. for the United States as Amicus Curiae at 28.

We would ordinarily be leery of an agency's view of what is essentially a legal issue, but we note that

in *Geier* the Supreme Court recently addressed the weight to be given to an agency's position on pre-emption. The Court "place [d] some weight" on a Department of Transportation interpretation, as set forth in an amicus brief, of a rule that it had promulgated. *Geier*, 529 U.S. at 883, 120 S.Ct. 1913. The Court considered that Congress had delegated the agency "authority to implement the statute; the subject matter is technical; and the relevant history and background are complex and extensive." *Id.* The Court stated that the agency was "‘uniquely qualified’ to comprehend the likely impact of state requirements." *Id.* (quoting *Lohr*, 518 U.S. at 496, 116 S.Ct. 2240). The Court also noted the consistency of the agency's position over time, *id.*, and the coherence of the agency's views, *id.* at 885, 120 S.Ct. 1913. Although the Court did not rely solely on the agency's position, it noted that "a specific expression of agency intent to pre-empt, made after notice-and-comment rulemaking" was not necessary to find conflict preemption. *Id.*

*17 [7] From *Geier*'s discussion of an agency's informal position regarding preemption, we conclude (1) that an agency's position concerning preemption need not be contained in a formal regulation in order*275 to be considered, and (2) that such a position is subject to a level of deference approximating that set forth in *Skidmore v. Swift & Co.*, 323 U.S. 134, 65 S.Ct. 161, 89 L.Ed. 124 (1944). Cf. *Christensen v. Harris County*, 529 U.S. 576, 587, 120 S.Ct. 1655, 146 L.Ed.2d 621 (2000) (quoting *Skidmore*, 323 U.S. at 140, 65 S.Ct. 161) (holding that agency interpretations contained in statements that "lack the force of law" are "‘entitled to respect’" only to the extent they have the "‘power to persuade’").^{FN21}

FN21. Counsel for GSK suggested that a combination of *Skidmore* and *Auer* deference was appropriate. Under *Auer v. Robbins*, 519 U.S. 452, 461, 117 S.Ct. 905, 137 L.Ed.2d 79 (1997) (citations and internal quotation marks omitted), an agency's interpretation of its own regula-

tion is "controlling unless plainly erroneous or inconsistent with the regulation." However, because the FDA purports to interpret both the statutory structure and regulatory framework, we believe it more prudent to apply *Skidmore* deference, which is the weaker of the two. This is also consistent with *Geier*, wherein the Court considered an agency's interpretation of its own regulation under a less deferential standard than that suggested by *Auer*. 529 U.S. at 883, 120 S.Ct. 1913.

"The fair measure of deference to an agency administering its own statute has been understood to vary with circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position." *United States v. Mead Corp.*, 533 U.S. 218, 228, 121 S.Ct. 2164, 150 L.Ed.2d 292 (2001) (alterations omitted) (citing *Skidmore*, 323 U.S. at 139-40, 65 S.Ct. 161).

It is important to consider the rationale given by the agency for its position that its actions preempt state law in the particular situation. In the case of the SSRI drugs at issue, Paxil, Zoloft, and the generic paroxetine manufactured by Apotex, the FDA has explained that "[u]nder-use of a drug based on dissemination of unsubstantiated warnings may deprive patients of efficacious and possibly lifesaving treatment. Further, allowing unsubstantiated warnings would likely reduce the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible." Br. for the United States as Amicus Curiae at 16-17. The FDA's view that "the imposition of liability under state law for defendants' alleged failure to warn would interfere with FDA's accomplishment of regulatory objectives," *id.* at 22, is in our view entitled to at least as much deference, if not more, as the FDA's view of its preemption authority. The Pennsylvania District Court accorded the FDA's views "significant" deference, *Colacicco*, 432 F.Supp.2d at 529, and we agree that in at least this

respect the FDA's view is entitled to some degree of deference.

In light of the circumstances in this case, we agree that the FDA's rejection of the warning plaintiffs proffer preempts a state-law action premising liability on a drug manufacturer's failure to include such a warning in the drug labeling notwithstanding that the agency's view was not subject to notice-and-comment rulemaking.

The Supreme Court has recently acknowledged the FDA's expertise in the context of the medical devices covered by the MDA. It stated, “[b]ecause the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the Act, the agency is uniquely qualified to determine whether a particular form of state law ‘stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,’ and, therefore, whether it should be preempted.” *Lohr*, 518 U.S. at 496, 116 S.Ct. 2240 (citing *276*Hines*, 312 U.S. at 67, 61 S.Ct. 399). Justice Breyer, concurring in that decision, also noted that the Court has “suggested that, in the absence of a clear congressional command as to pre-emption, courts may infer that the relevant administrative agency possesses a degree of leeway to determine which rules, regulations, or *other administrative actions* will have pre-emptive effect.” *Id.* at 505, 61 S.Ct. 399 (Breyer, J., concurring) (emphasis added) (citing cases). Of course, the FDA is equally expert, if not more so, with respect to regulation of drugs, with which it has had a longer experience than with medical devices.

*18 We need not decide whether the FDA's position in this case is inconsistent, as plaintiffs argue, with the FDA's 2000 rule proposal. We see no inconsistency between the FDA's preamble to the 2006 amendments and its long-held position that it has the responsibility to determine whether a warning is required. Compare44 Fed.Reg. at 37,447 (stating, in 1979, that “the decision as to whether a warning is legally required for the labeling of a drug must rest with the agency”), with71 Fed.Reg. at 3934

(“In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act.”).

In conclusion, based on our own review of the FDCA, the FDA's regulations, and the FDA's actions taken pursuant to its statutory authority, we conclude that the failure-to-warn claims brought by Colacicco and McNellis conflict with, and are therefore preempted by, the FDA's regulatory actions. It is important to note that we express no view as to the merits of the issue whether SSRIs contribute to adult suicidality. We are not scientists and we do not purport to have any expertise on that issue. That is within the FDA's authority. This decision is based on the record before us.

V.

For the above-stated reasons, we will affirm the judgment of the United States District Court for the Eastern District of Pennsylvania dismissing Colacicco's complaint and we will reverse the order certified by the United States District Court for the District of New Jersey with instructions that judgment be entered in favor of the defendants. In light of our decision with respect to preemption, we need not reach the other issues considered by the District Courts.

AMBRO, Circuit Judge, dissenting.

The majority opinion describes these cases as situations calling for preemption: the expert agency, the Food and Drug Administration (“FDA”), consults scientific data to generate the optimal warnings (not too lax, not too alarmist) for drug labels and state tort lawsuits would disrupt this fine system. But there is an important contrary view that has prevailed until recently: state tort law complements FDA provisions on drug warnings, in part by eliciting more information than the FDA would glean otherwise from pharmaceutical manufacturers. This contrary view has, I believe, the better argument in terms of legal doctrine on preemption, congressional intent, and the history of state tort

law alongside federal law. Although the majority opinion is well-crafted and responsibly narrow, I would not move even the short distance my colleagues go toward preemption of state-law torts. I thus respectfully dissent.

I. Presumption Against Preemption

The majority opinion begins its analysis where I would, by examining whether we are to apply a presumption against preemption. State tort law, dealing with failure-to-warn claims (like those brought by *277 the plaintiffs in our cases), addresses health and safety and thus falls within the states' traditional police powers. See *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996) (describing the presumption against preemption and asserting "the historic primacy of state regulation of matters of health and safety"). As the majority recognizes, the presumption does not always apply; for example, it does not apply to claims alleging fraud on the FDA. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-48, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001). That the presumption there does not apply—where common sense points to federal law governing exclusively those who seek to defraud a federal agency—is no surprise, and hardly weakens the presumption when it does apply.

*19 The presumption against preemption must inform our analysis of both "whether Congress intended any pre-emption at all" and "the scope of its intended invalidation of state law." *Lohr*, 518 U.S. at 485, 116 S.Ct. 2240 (emphasis omitted). When the presumption applies, rebutting it requires a clear expression that Congress intended to preempt. *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449, 125 S.Ct. 1788, 161 L.Ed.2d 687 (2005) ("In areas of traditional state regulation, we assume that a federal statute has not supplanted state law unless Congress has made such an intention clear and manifest.") (citations and internal quotation marks omitted).

In my view, the majority opinion under-emphasizes congressional intent as the "ultimate touchstone of pre-emption analysis." *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516, 112 S.Ct. 2608, 120 L.Ed.2d 407 (1992) (citations and internal quotations marks omitted). Our inquiry is "guided" by a focus on gaining "a fair understanding of congressional purpose." *Lohr*, 518 U.S. at 485-86, 116 S.Ct. 2240 (quoting *Cipollone*, 505 U.S. at 530, 112 S.Ct. 2608) (emphasis in original). As the majority opinion rightly recognizes, the defendants in our cases do not make a serious argument that this case involves express preemption or field preemption. But I would place more significance on the fact that the key *conflict* preemption cases that the majority opinion relies on involve express statutory preemption provisions. *Geier v. American Honda Motor Company*, 529 U.S. 861, 864-65, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000) (evaluating viability of state-tort-law claims in light of a preemption provision, 15 U.S.C. § 1392(d), and a savings provision, *id.* § 1397(k), within the National Traffic and Motor Vehicle Safety Act of 1966); *Lohr*, 518 U.S. at 481, 116 S.Ct. 2240 (evaluating viability of state-tort-law claims in light of the preemption provision of the Medical Devices Act, 21 U.S.C. § 360k(a)).

Even when considering a species of implied pre-emption-as conflict preemption generally is, see *Geier*, 529 U.S. at 884, 120 S.Ct. 1913—we should be asking whether Congress intended to preempt. In our cases, we have no statutory preemption provision to interpret that relates to drug labeling in the Food, Drug and Cosmetic Act ("FDCA"). This fact should push us to hold the presumption against preemption in place, as we lack the best kind of evidence of congressional intent: statutory text.

The absence of a relevant preemption provision in the FDCA does not, of course, resolve whether the presumption against preemption is overcome by something else. The Supreme Court has "held repeatedly that state laws can be pre-empted by federal regulations as well as by federal statutes." *Hillsborough County v. Automated Med. Labs.*, 471 U.S.

707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985). Although initial approval of drug labeling involves *278 both statutory and regulatory provisions, FDA regulations primarily govern the continuing oversight of drug-label revisions. These regulations, at the time relevant to this litigation, required drug manufacturers to revise labeling “to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug,” 21 C.F.R. § 201.57(e), and to submit supplemental information in the event that they “add or strengthen a contraindication, warning, precaution, or adverse reaction,” *id.* § 314.70(c). The defendants in our cases rely primarily on their continuing obligations under these FDA regulations for their conflict-preemption argument.

*20 Yet the mere presence of a comprehensive regulatory scheme such as the FDA’s for drug labeling does not itself unseat the presumption against preemption. *Hillsborough County*, 471 U.S. at 717, 105 S.Ct. 2371 (“We are even more reluctant to infer pre-emption from the comprehensiveness of regulations than from the comprehensiveness of statutes.”).^{FN22} Because our focus must remain on congressional intent, we should remember in deciding questions of *regulatory* preemption that any inferences regarding congressional purpose typically will be indirect. Congress enacted the FDCA, which in turn enabled the FDA to adopt its regulations regarding continuing (*i.e.*, post-approval) drug labeling. To overcome the presumption against preemption, the defendants in our cases must show that Congress implicitly intended to allow the FDA to adopt regulations that preempt failure-to-warn lawsuits under state law. Cf. *Fidelity Federal Sav. & Loan Ass’n v. de la Cuesta*, 458 U.S. 141, 162, 102 S.Ct. 3014, 73 L.Ed.2d 664 (1982) (holding that Federal Home Loan Bank Board regulations preempted state law where “the statutory language suggests that Congress expressly contemplated, and approved, the Board’s promulgation of regulations superseding state law” after also inquiring into the Board’s own intent to preempt).

FN22. The majority opinion suggests that, because *Hillsborough County* considered field preemption in analyzing the municipal ordinances at issue, the operation of the Supreme Court’s application of the presumption against preemption in that case “is not clear.” I disagree with this suggestion. *Hillsborough County*’s discussion of the presumption against preemption appears in Part III of that opinion. 471 U.S. at 714-16, 105 S.Ct. 2371. The field-preemption analysis in Sections IV.A and IV.B, and the conflict-preemption analysis in Section IV.C, follow. *Id.* at 716-20, 105 S.Ct. 2371. In my view, the Court’s purpose in setting out the presumption against preemption in Part III was to indicate that the presumption should guide the analysis in all sections of Part IV.

The majority opinion closes its discussion of the presumption against preemption by describing a “tension” between the presumption as outlined in *Lohr* and some seemingly contrary language in *Geier*. But the *Geier* side of this doctrinal tug-of-war has slippery footing. The quoted language “[O]ne can assume that Congress or an agency ordinarily would not intend to permit a significant conflict,” *Geier*, 529 U.S. at 885, 120 S.Ct. 1913—appears as a *dictum* in the context of a larger discussion of whether an agency must adopt a clear statement of preemptive intent for a conflict between federal regulation and state law to exist.^{FN23} This sentence does *279 not create a counter-presumption in favor of preemption, for the very next sentence in *Geier* states that “a court should not find pre-emption too readily in the absence of clear evidence of a conflict.” *Id.* That is a restatement of the presumption against preemption, suggesting that we should not interpret *Geier* to muddy the presumption or to dilute its effect.^{FN24}

FN23. That discussion in *Geier* settles the issue: an agency need not do so for a conflict to exist. 529 U.S. at 884-85, 120 S.Ct.

1913. Even without express statutory preemption or a clear agency statement on preemption, a court may find that state law “actual[ly] conflict[s]” with federal law under the facts of a particular case. *Id.* at 884, 120 S.Ct. 1913 (quoting *English v. Gen. Elec. Co.*, 496 U.S. 72, 79, 110 S.Ct. 2270, 110 L.Ed.2d 65 (1990)). I address the broader issue of how much deference we owe an agency’s position on preemption below. See *infra* Part II.

FN24. In contrast, the majority opinion never again mentions the presumption against preemption after Section IV.A of its opinion, suggesting that the presumption is performing virtually no analytical work.

When a federal court undertakes a conflict-preemption analysis, a “significant conflict” between federal and state law might be the kind of “clear evidence” that could rebut the presumption against preemption. *Geier*, 529 U.S. at 885, 120 S.Ct. 1913. We can assume Congress or the FDA had awareness of products-liability law when legislating or regulating. So if we find a genuine conflict, we may conclude that Congress intended to preempt state law. But in situations involving less obvious conflicts, the presumption against preemption will be more difficult to overcome.

I would apply the presumption against preemption here. The plaintiffs’ failure-to-warn claims stand near the heart of the states’ police powers over matters of health and safety. And the existence and detailed nature of the federal scheme does not change our imperative to require clear congressional intent (whether expressed directly in a preemption provision or implied by an authorizing statute enabling an agency to act) to preempt state tort law.

II. Deference to the FDA’s View on Preemption

*21 At the end of its conflict-preemption analysis-

even after addressing the plaintiffs’ arguments—the majority opinion considers the FDA’s own view regarding the preemptive effect of its drug-labeling regulations. In 2006, the preamble to an FDA revision of its drug-labeling regulations stated that failure-to-warn claims are preempted if, at the time of injury, the substance of the alternative warning proposed by plaintiffs (1) had already been submitted to the FDA and (2) had not been adopted. 71 Fed.Reg. 3922, 3936 (Jan. 24, 2006). The FDA also filed an *amicus* brief in the *Colacicco* case before us, arguing that “federal law preempts a state tort claim arising out of drug manufacturers’ alleged failure to provide a warning that FDA determined was not scientifically supported.” FDA Br. 16. The FDA emphasizes that it strives for the optimal strength of warning. Anything less or more than the FDA-approved and FDA-monitored warning, in the agency’s view, would be “false or misleading.” See 21 U.S.C. §§ 331(a)-(b), 352(a); Br. of *Amicus Curiae* United States at 2.

We must decide what weight we should give to these FDA views before analyzing the purported conflict in this case. I agree with the majority opinion that we should apply *Skidmore* deference to the FDA’s informal position contained in its 2006 preamble and its *amicus* brief in *Colacicco*. See *Geier*, 529 U.S. at 883, 120 S.Ct. 1913 (placing “some weight” on the Department of Transportation’s interpretation of its own airbag regulation); *Skidmore v. Swift & Co.*, 323 U.S. 134, 139, 65 S.Ct. 161, 89 L.Ed. 124 (1944) (giving the Department of Labor’s “interpretive bulletin” regarding the calculation of working hours a level of deference based on “all those factors which give it power to persuade, if lacking power to control”). The formulation in *Mead*, which cites *Skidmore* and which the majority opinion quotes, *280 designates the following factors for consideration: “the degree of the agency’s care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency’s position.” *United States v. Mead Corp.*, 533 U.S. 218, 228, 121 S.Ct. 2164, 150 L.Ed.2d 292 (2001).

I disagree with the majority opinion, however, in its application of the standards articulated in *Skidmore* and *Mead*. Comparing FDA statements from 1979 and 2006, my colleagues discern “no inconsistency” between them.^{FN25} I suggest a better analysis of inconsistency would take a more detailed view of the FDA’s position(s) during the 27 intervening years.^{FN26} For instance, only slightly more than seven years ago the FDA disavowed any “federalism implications” or preemptive effect of changes to its requirements for prescription drug labeling. 65 Fed.Reg. 81,082, 81,103 (Dec. 22, 2000). Rather than maintaining a consistent position, the FDA now undertakes a “180-degree reversal.” David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 474 n. 59 (2008) (internal quotation marks omitted). Its current position is novel rather than longstanding. See id. at 462 (“For most of its seventy-seven-year history [since receiving the name “Food and Drug Administration” in 1930], the [FDA] has regulated the drugs sold in the United States without any significant interaction with the world of state-law damages litigation.”). I thus conclude that the FDA’s position regarding preemption deserves little deference by way of its inconsistency.

FN25. Importantly, the majority opinion’s quote from the 1979 regulation is taken out of context. Rather than contemplating the FDA’s relation to state courts, the quoted sentence discusses the FDA’s relation to panels of experts from which the agency seeks advice: “Although FDA often refers questions of whether a warning should be included in the labeling of a drug to its standing advisory committees, the decision as to whether a warning is legally required for the labeling of a drug must rest with the agency.” 44 Fed.Reg. 37,434, 37,447 (June 26, 1979) (emphasis added). Thus there is no support I can find in the record for the proposition that, in 1979, the FDA viewed its drug-labeling regulations as preemptive

of state tort law.

FN26. Some Supreme Court cases suggest that inconsistency is no bar to deference. See, e.g., *Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 103 S.Ct. 2856, 77 L.Ed.2d 443, 42 (1983). But others have language suggesting that inconsistency counts against the agency’s position. See, e.g., *Bates*, 544 U.S. at 449, 125 S.Ct. 1788 (finding a preemption argument “particularly dubious” in light of the EPA’s change in position within five years).

*22 The majority opinion relies on another of the *Skidmore* and *Mead* factors: agency expertise. Undoubtedly, the FDA has special expertise in evaluating the scientific evidence on pharmaceuticals’ safety and efficacy. That expertise should contribute to any consideration of the proper mix of legal institutions used to regulate drug labeling. But, as my colleagues note, “[w]e would ordinarily be leery of an agency’s view of what is essentially a legal issue.” The FDA is not an expert on federalism concerns. Nor is the agency the only Government institution that should bring its perspective to bear on the relationship between the executive branch and state courts; Congress, federal courts, and state courts each have a constitutional responsibility under the Supremacy Clause to evaluate such issues. Thus, I would consider the FDA’s expertise only a mild positive in our calculation of how much deference to apply in these cases.

The remaining factors listed in *Mead* weigh against giving the FDA’s view on preemption much deference. With respect to “formality,” the FDA has not engaged *281 in notice-and-comment rulemaking on this issue, instead promulgating its views in a preamble to a regulation and a series of *amicus* briefs in cases like these. As the majority notes, notice-and-comment rulemaking is not *required* to find conflict preemption. See *Geier*, 529 U.S. at 885, 120 S.Ct. 1913. But the lack of notice-and-comment rulemaking should, all else equal, re-

duce the level of deference we give the FDA's position. Similarly, the lack of institutional formality suggests a relatively low "degree of care" taken to outline its reasoning.^{FN27} In my view, a high degree of care on issues of preemption would involve scholarly, scientific, and public-health^{FN28} research into the complex matters of law and policy that these cases implicate. I see no evidence in the record that the FDA conducted or commissioned independent research of this nature in preparing the 2006 preamble.

FN27. By making this point I do not mean to criticize FDA counsel's efforts in writing its *amicus* brief in this case or at oral argument. On the contrary, counsel performed admirably in both regards. My focus here is in-depth institutional research on law and policy preceding the recent "about face" on agency preemption.

FN28. A group of public health researchers writes that "[i]ndirect regulation of the pharmaceutical industry by tort litigation is an important complement to the regulation of drug safety by the FDA." Br. of *Amicus Curiae* Curt D. Furberg, M.D., Ph.D., et al. at 6. This view-based on various scholarly, peer-reviewed articles-does not receive any attention in the 2006 preamble or in the FDA's *amicus* brief. Notice-and-comment rulemaking would provide a forum for such research to be considered, but, as noted, the FDA has not undertaken that administrative process on the issue of preemption of state tort law.

In summary, the *Mead* factors counsel us to give the FDA's position a relatively low level of deference. The ultimate test under *Skidmore* is nonetheless whether the FDA's (and the defendants') view has the "power to persuade," 323 U.S. at 139, 65 S.Ct. 161, an evaluation I take up in Part III.

III. Conflict Preemption.

The defendants' argument is that labeling that satisfies the FDA is both the minimum and the maximum amount of labeling they may do. Under this view, the FDA believes it has struck the proper balance between safety and efficacy, that is, between avoiding unintended injuries to patients because of insufficient warnings while not deterring too many patients from using drugs that would benefit them because of unjustified over-warnings. Adding additional warnings unsupported by medical evidence would subject the defendants to FDA sanctions for false labeling. Conflict preemption must apply to block state-law claims for failure to warn, according to the defendants, since stronger warnings for Paxil and Zoloft-the drugs within the category of selective serotonin reuptake inhibitors ("SSRIs") involved in these cases-would violate FDA regulations. This makes it impossible, defendants continue, for them to have complied with both state and federal law. Alternatively, imposing an overlay of tort liability would frustrate the federal objective of having the FDA strike the safety-efficacy balance.

*23 For the reasons I describe below, I disagree with this characterization of the interaction of FDA regulation and state tort law. Informed by the presumption against preemption, I see the federal and state constructs as complementary, as they have been since the 1930s. The majority opinion's holding of preemption in these cases, despite an apparently narrow construction, threatens the institutional framework we have for balancing safety and efficacy in *282 the pharmaceutical industry while compensating victims of wrongful injuries.

A. Absence of an Actual Conflict

None of the drug manufacturers in these cases attempted to enhance a warning and received an FDA sanction in response. The majority opinion correctly states that hypothetical conflicts can give rise to conflict preemption. But the hypothetical in question must be convincing for us to allow this. The conflict the defendants raise relies, at its heart, on the FDA punishing drug manufacturers for over-

warning. But a heightened warning would likely have its source in new information that the FDA had not previously known. Thus, I find it hard to believe that, if a drug manufacturer augmented its warning in response to or in anticipation of a state tort lawsuit, the FDA would sanction the manufacturer for over-warning consumers under 21 U.S.C. §§ 331(a)-(b) and 352(a).

Indeed, drug manufacturers have authority to strengthen warnings without advance permission from the FDA. The plain language of 21 C.F.R. § 314.70 permits unilateral additions to warnings, subject to subsequent FDA approval: “[T]he holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change,” including such changes as “add[ing] or strengthen[ing] a contraindication, warning, precaution, or adverse reaction.” 21 C.F.R. §§ 314.70(c)(6), (c)(6)(iii)(A). The motivation for additional warnings, which the regulation does not address, need not come from inside the pharmaceutical company in question or FDA prodding. In particular, that motivation may come from a failure-to-warn lawsuit or the threat of one.

Drug manufacturers have the best information about the safety of their products. The FDA does not conduct its own drug trials and “does not have sufficient authority to require additional clinical trials after drug approval.” Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 B.C. L.Rev. 1089, 1149 (2007). Thus, to avoid discouraging the party with the best safety information from coming forward, 21 C.F.R. § 314.70 permits a manufacturer to alter a drug label before the FDA has evaluated and approved the change.

The defendants and the FDA do not cite even one example of the FDA punishing a drug manufacturer for over-warning. See Oral Argument Tr. 82, Dec. 10, 2007 (statement of FDA counsel that she was “not aware of any instance” in which the FDA “told a manufacturer who added an increased warning

that that warning was unsubstantiated and caused the drug to be misbranded”).^{FN29} At oral argument, counsel for GlaxoSmithKline mentioned that, in 2004, the FDA required additional language in response to a strengthened warning by Wyeth Pharmaceuticals in a “changes being effected” supplement under 21 C.F.R. § 314.70. Merely requiring a clarification of or addition to warning language does not strike me as close to being close to a true conflict. On the contrary, the Wyeth example shows that the FDA typically engages in a back-and-forth discussion with drug manufacturers about warnings. In the event of a state tort lawsuit resulting in a warning that conflicted*283 with the FDA’s previous judgment, a commonplace dialogue between the manufacturer and the FDA could produce a warning complying with both federal regulations and state tort law.

FN29. The majority opinion emphasizes a different fact: that the FDA, in response to citizen petitions and approvals of new uses for existing SSRIs, considered requiring a strengthened warning and declined. I agree that inaction of this kind is a form of agency action. But more important to me is that the FDA may never have sanctioned a drug manufacturer that strengthened a warning without prior FDA approval. This additional example of FDA inaction suggests that the conflict complained of is not an actual conflict.

B. Harmony Between Tort Law and FDA Regulation

*24 Tort law and FDA regulation do not have conflicting goals. Both seek to strike a safety-efficacy balance. Under a negligence standard, most state courts balance the cost of care owed to a patient against the prospective harm. See, e.g., *La Russa v. Four Points at Sheraton Hotel*, 360 N.J.Super. 156, 821 A.2d 1168, 1173-74 (2003) (quoting Judge Learned Hand’s formula from *United States v. Carroll Towing Co.*, 159 F.2d 169, 173, reh’g denied, 160 F.2d 482 (2d Cir.1947), which com-

pare the cost of precautions with the expected loss); *cf.* Stephen G. Gilles, *On Determining Negligence: Hand Formula Balancing, The Reasonable Person Standard, and the Jury*, 54 Vand. L.Rev. 813, 816-22 (2001) (describing widespread use of, as well as complications in applying, the Hand formula).

Properly understood, the cost of additional warnings includes the consequences of over-warning that the defendants emphasize and that the FDA similarly takes into account.^{FN30} In reaching its holding of conflict preemption, the majority focuses on the hypothetical scenario of differing (and presumably conflicting) results of the FDA regulatory process and state tort lawsuits. Because we are dealing with hypothetical situations, however, I would focus on the essential harmony of the standards applied by the FDA and state courts rather than the disharmony conjured about the results. Both institutions seek to balance safety and efficacy. If it turns out those results actually conflict, then it is time for Congress to step in or at least for the FDA to propose a rule followed by public comment before proclaiming preemption.

FN30. Advocates of preemption in these cases point to the danger of “over-warning” and imply that over-warning will result from jury decisions biased toward plaintiffs. Br. of *Amicus Curiae* Product Liability Advisory Council, Inc. at 14-23. This argument assumes that juries do not understand that the cost of care, including the cost of taking too much care, is part of determining negligence. I presume, for the purposes of analyzing a hypothetical conflict between federal and state law, that state-court judges will properly instruct juries about the negligence standard.

Allowing multiple institutions to investigate the difficult question of how strong to make a warning can have important benefits. State courts provide a check on agency power. Our society relies on the

FDA to an enormous degree to monitor the safety of pharmaceuticals. But the FDA's toolkit is imperfect and incomplete by design. The FDA relies on the information provided by drug manufacturers (to repeat, it does no independent testing), and will always lack the inside perspective on clinical trials and data analyses stemming from those trials. Moreover, the FDA is limited as to the additional clinical trials it may require post-approval, Davis, *supra*, at 1149 & n. 444, and even “the reporting process for postapproval adverse reaction events ... is too weak,” *id.* at 1149 & n. 443. Also, as they play their parts in the post-approval process the drug manufacturer and the FDA will not necessarily ask the right questions. The citizen-petition administrative process was used here unsuccessfully to seek an FDA requirement of stronger warnings for SSRIs. Discovery in state tort lawsuits provides a different way for third parties to raise questions about new and existing drugs. Given this context, I would not eliminate the potentially*²⁸⁴ valuable information-gathering tools of state tort law.

To make all this real, I would point out that the regulatory process at the FDA, even if it allows for submission of citizen petitions, does not compensate the families of alleged victims like Lois Colacicco and Theodore DeAngelis. The availability of damages in state tort lawsuits can give injured citizens the incentive to come forward and share potentially valuable information. Even if an injury or death turns out not to have been caused by a drug or an insufficient warning, that information, too, can have social value. And the prospect of paying damages can sharpen drug manufacturers’ incentives to place appropriate weight on safety as they strike the safety-efficacy balance. We should not lightly assume this balance now preempted-and by a single recently adopted preamble at that.

C. Backdoor Federalization

*²⁵ The FDA's position in these cases is an instance of “backdoor federalization,” a descriptive term commentators have recently used to describe a

trend in the federal courts toward finding state law preempted. On the positive side, centralized federal control can facilitate uniform regulation of a national market (like that for pharmaceuticals) and prevent states from interfering with the affairs of other states. Samuel Issacharoff & Catherine M. Sharkey, *Backdoor Federalization*, 53 UCLA L.Rev. 1353 (2006).

Unfortunately, the trend toward federalization is not fully benign. While the FDA seeks to keep private plaintiffs out of state court (or federal court applying state law in diversity actions), a separate line of jurisprudence has limited private rights of action. There is a “troublesome” contrast in the way courts now tend to “grant agencies expansive discretion to interpret or declare the preemptive scope of the regulations they promulgate, whereas agencies are not given corresponding latitude to infer private rights of action under those same regulations.” Catherine M. Sharkey, *Preemption by Preamble: Federal Agencies and the Federalization of Tort Law*, 56 DePaul L.Rev. 227, 258-59 (2007).

Although the FDA should have a strong voice in the debate among government institutions about preemption of state tort law, by executive order it must consult with state and local governments about the consequences of its regulations. *See id.* at 252-55 (citing Exec. Order No. 13,132, 64 Fed.Reg. 43,255, 43,257 (Aug. 10, 1999)). But nothing in the record suggests a dialogue between federal and state officials has occurred regarding preemption of failure-to-warn lawsuits.

I would interpret the absence of an express preemption statute, the text of the actual FDA regulations, and the late arrival of the FDA's statement on preemption in a preamble, as evidence that state tort law is not displaced. Tort lawsuits can generate useful information that the FDA can inject into its regulatory process. And tort damages can aid the FDA in aligning drug manufacturers' incentives to find the right balance between safety and efficacy. In any event, the choice to preempt state tort law is best left to Congress, should it wish to do so. In these

cases, I do not see the kind of conflict that implies Congress has made that choice.

IV. Conclusion

The plaintiffs allege that SSRIs increase the risk of patients committing suicide. They further allege that the drug manufacturers knew or should have known this, but failed to label their products appropriately. The defendants would have us halt any inquiry into their alleged negligence before it starts. They contend that, in the *285 area of drug labeling, state tort law renders compliance with federal provisions impossible, or at least stands as an obstacle to federal objectives.

The FDA, which relies on information provided by others, seeks to stop one avenue of information—that gathered from suits under state tort law theories. But should an earlier series of FDA decisions indicating that the previous warnings were adequate, when they might be inadequate, preclude the operation of state tort law? The majority suggests that the plaintiffs' claims border on claiming fraud on the FDA. But the underlying issue in these preemption cases is the structure of federal-state relations. We must decide whether the FDA will be the sole decision-maker. Without a clear statement from Congress or clear evidence that state law “stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,” *Hines v. Davidowitz*, 312 U.S. 52, 67, 61 S.Ct. 399, 85 L.Ed. 581 (1941), I am reluctant to say that the defendants' claim of a conflict has sealed the presumption against preemption.

*26 A holding of no preemption in these cases would not suggest in any way that the defendant drug manufacturers should be liable for plaintiffs' injuries. Like my majority colleagues, I express no view regarding the relationship between SSRIs and adult suicide. Allowing the plaintiffs' cases to proceed beyond the motion-to-dismiss stage means instead that the state courts and federal district courts applying state tort law may evaluate—provide a

check on whether the FDA struck the right balance in the precautions and warnings it required for SS-RIs.

To review the history of this issue, the FDA has for over three-quarters of a century viewed state tort law as complementary to its warning regulations. Only for the last two years has it claimed otherwise. This "sea change," Sharkey, *supra*, at 242, in the FDA's conception of the relationship between federal and state law has not appeared in a regulation subject to notice and comment, but in a preamble to a regulation. With this background, I believe courts should fear to tread where Congress has not given us a clear statement. Because I see sound legal and policy reasons to hold that the presumption against preemption is not overcome, I would allow the plaintiffs' suits to go forward. I respectfully dissent.

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